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ADSORPTION OF INFLUENZA VIRUS[1]

BY RONALD HARE[2] AND MARJORIE CURL[3]

Abstract

Influenza A and B viruses in allantoic fluid can be adsorbed by certain grades of diatomaceous earths usually employed as filter aids, there being a marked degree of correlation between the 'flow rate' of the earths and their ability to adsorb the virus. Of the clays, kaolin and fuller's earth are similarly able to adsorb the virus as are certain varieties of charcoal. Elution of the adsorbed virus is also possible provided a protein-containing solution such as broth, serum, or isinglass be employed, the highest yield being obtained with virus adsorbed on silica earths and eluted with isinglass solution.

Introduction

Since the discovery of the adsorption of influenza virus by red cells and its elution with saline, this method has been extensively employed for the manufacture of vaccine. For various reasons, it seemed advisable to investigate other adsorbing agents that could be sterilized and that, unlike red cells, would not be damaged by formalin. This forms the subject of the present communication.

Methods

Source of Virus

Using the PR8 strain for influenza A virus and the Lee strain for influenza B virus, living fertile eggs were inoculated on the 12th day with living virus. Pools of allantoic fluid containing either A or B virus were harvested 48 hr. later under sterile conditions and kept in the refrigerator at 4° C. until used.

Adsorption

Five or 10 cc. quantities of allantoic fluid containing virus were added to weighed amounts of the adsorbent under test, the tubes were allowed to come to the required temperature, thoroughly mixed, and shaken frequently for a suitable interval. They were centrifuged and the supernatants removed for titration. The percentage adsorbed was calculated by comparison of pool and supernatant titres.

Elution

A volume of the eluent under test was added to the adsorbent with its attached virus, the contents brought to the desired temperature, and shaken

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for a suitable time. The tubes were again centrifuged and the supernatants removed for titration. By comparing these titres with the pool titres the over-all yield was calculated.

Titrations

These were carried out by the red cell method of Hirst (4), using washed chicken cells from the slaughter house. The readings were taken after 75 min. at room temperature, the end point being taken as the tube with a supernatant opacity midway between that of tubes containing 0.5 and 0.75% red cells. The titre of the fluid is the reciprocal of the dilution at the end point.

Experimental

Adsorption with Silica Earths

In the first experiments a series of filter aids, made by Johns-Manville, were employed. Adsorption was attempted by adding 5 cc. of allantoic fluid containing PR8 virus to 0.2 gm. samples of the filter aids in 4 × ½ in. test tubes. A parallel series was set up using fluid whose pH (which is normally 8.6) had been modified to 7.0 by the addition of normal hydrochloric acid. Both series of tubes were shaken for 15 min. at room temperature, centrifuged, and the supernatants removed for titration by agglutination of red cells.

The results given in Table I indicate that there is a considerable difference in the ability of these substances to adsorb influenza virus, there being an

TABLE I

ADSORPTION OF INFLUENZA A VIRUS BY SILICA ADSORBENTS

Adsorbent	pH 7.0		pH 8.6	
	Titre of supernatant	% Adsorbed	Titre of supernatant	% Adsorbed
Pool unadsorbed	512	—	512	—
J-M Filteraids				
Celite Filter-Cel	<8	100	<8	100
Celite 505	64	87	128	75
Celite 535	256	50	384	25
Celite 512	256	50	512	0
Celite Hyflo Super-Cel	256	50	512	0
Celite 501	512	0	512	0
Celite 503	512	0	512	0
Other Filteraids				
Dicalite Superaid	<8	100	<8	100
Superfiltrol	128	75	96	81
Other Substances				
Silicic acid	96	81	192	62
Florite	512	0	512	0
Sand	512	0	512	0

Note: Titres represent the reciprocal of the dilution at the end point. Percentage adsorption calculated from the titres of the pool and the supernatant after adsorption.

apparent connection between the particular grade employed and its ability to remove the virus. When the pH of the fluid was modified towards neutrality, two of these substances were able to adsorb some virus and a third became more efficient.

These filter aids are all produced from diatomaceous earths but being calcined to a greater or lesser extent in the course of their preparation, this treatment causes glazing of the surface and some fusion of particles. The degree to which this occurs would seem to be responsible for variation in the 'flow rate' of the substance, this being the rate at which a given sludge passes through a filter press charged with the substance under test. The substance with the lowest 'flow rate' is Celite Filter-Cel and in order of increasing magnitude Celite 505, Celite 512, Celite Hyflo Super-Cel, Celite 501, Celite 503, and Celite 535, the last being the substance with the highest 'flow rate'. In Table I it can be observed that Celite Filter-Cel removed most virus, to be followed in order by Celite 505, Celite 535, Celite 512, Celite Hyflo Super-Cel, Celite 501, and Celite 503. This order is almost identical with that of their 'flow rates', although for some as yet undetermined reason, Celite 535 is out of place, its powers of adsorption being fairly high despite the fact that its flow rate is also high.

The decrease in adsorption with increasing 'flow rate' can be attributed either to the decrease in available surface or to the diminished 'pore size', which is presumably a measure of the size of the spaces between the particles. It is not yet possible to determine which of these explanations, if either, is responsible for the gradation of the adsorptive properties, but it would seem that the loss of available surface was most probable.

In Table I also it can be seen that adsorption with Dicalite Superaid, the only available representative of a similar series of filter aids distributed by the MacArthur Chem. Co., corresponded to that of Celite Filter-Cel, while Superfiltrol (thiamin grade) produced by the Filtrol Corp. behaved in the same way as Hyflo Super-Cel and Celite 512.

Several other silica substances—Florite (a silica desiccant produced by the Floridin Co.), Baker's silicic acid, and Cenco white sand—were investigated in this group, but Florite and sand failed to adsorb any virus while silicic acid showed adsorptive properties similar to those of Superfiltrol, Hyflo Super-Cel, and Celite 512.

Adsorption with Clays or Aluminium Silicate Earths

Kaolin (BDH and Merck), fuller's earth (BDH), Lloyd's reagent (Eli Lilly) and also adsorptive alumina (Fischer Chem. Co.) were tested at pH 7.0 and pH 8.6 in a manner similar to the silica adsorbents. The results given in Table II indicate that these substances, with the exception of alumina, are able to adsorb the virus completely.

Adsorption with Charcoals

The third series of adsorbents included five charcoals: Norrit A, decolorizing (Baker), bone (Baker), Clifchar (CIL), and Nuchar (West Virginia Pulp

TABLE II

ADSORPTION OF INFLUENZA A VIRUS BY CLAYS

Adsorbent	pH 7.0		pH 8.6	
	Titre of supernatant	% Adsorbed	Titre of supernatant	% Adsorbed
Pool unadsorbed	512	—	512	—
Kaolin (Merck)	8	99	16	97
Kaolin (BDH)	<8	100	<8	100
Fuller's earth	<8	100	<8	100
Lloyd's reagent	<8	100	<8	100
Alumina	384	25	512	0

Note: Percentage adsorption calculated as in Table I.

TABLE III

ADSORPTION OF INFLUENZA A VIRUS BY CHARCOALS

Adsorbent	pH 7.0		pH 8.6	
	Titre of supernatant	% Adsorbed	Titre of supernatant	% Adsorbed
Pool unadsorbed	512	—	512	—
Clifchar	512	0	512	0
Nuchar	<8	100	16	97
Bone charcoal	64	87	64	87
Decolorizing	12	98	<8	100
Norrit A	16	97	<8	100

Note: Percentage adsorption calculated as in Table I.

and Paper Co.). With the exception of Clifchar, a lumpy rather than a powdered charcoal, all removed more than 90% of the virus at both pH 7.0 and pH 8.6.

Adsorption with Miscellaneous Substances

Besides these regular adsorbents a series of miscellaneous substances, including alundum, asbestos, talcum, starch, filter paper pulp, adsorbent cotton, and glass wool, was investigated but there was no adsorption.

Conditions for Maximum Adsorption

Because the adsorptive forces are lowest in diatomaceous earths it would seem probable that elution of adsorbed virus from these substances would be easier. Since Filter-Cel and Superaid were the most efficient of the group they were chosen for further investigations.

In the first experiments the weight of adsorbent necessary for complete adsorption was determined. Quantities of dry powder varying from 0.01 gm. to 0.40 gm. were shaken continuously with 5 cc. of allantoic fluid at 0° C.

for 5 to 10 min., previous investigations having shown that it was necessary to keep the Superaid suspended in the medium for at least five minutes to get consistent results. Increasing the time beyond this increased the adsorption but only very slightly. From the results of several experiments carried out in this way, one of which is given in Table IV, it would seem that 0.2 to 0.25 gm. of Superaid in 5 cc. of fluid was sufficient for almost complete adsorption. Above this the increase in adsorption with increasing weight was slight.

TABLE IV

EFFECT OF WEIGHT OF DICALITE SUPERAID ON ADSORPTION OF INFLUENZA A VIRUS

Weight of Superaid	Supernatant titre	% Adsorbed
0.00	256	—
0.025	256	0
0.05	256	0
0.10	96	62
0.15	32	88
0.20	32	88
0.25	16	94
0.30	12	96
0.40	<8	100

Note: Adsorption from 5 cc. of infected allantoic fluid. Percentage adsorption calculated as in Table I.

Adsorption is usually more efficient at low temperatures and for this reason the earliest work was carried out at 0° C. From numerous experiments, however, it would appear that temperatures between 25° C. and 37° C. gave slightly more complete adsorption, although the effect of temperature was in no case very pronounced.

From these investigations it would seem that 0.2 gm. of Superaid shaken continuously for five minutes at room temperature adsorbed most of the virus present in 5 cc. of allantoic fluid.

As far as could be determined from preliminary experiments, the optimum conditions for adsorption by Filter-Cel were approximately the same as those for Superaid.

There can be little doubt that this is a true adsorption because Superaid with its adsorbed virus can be washed in successive changes of saline, the washings showing no more that a trace of virus. Moreover, as will be shown, it is possible to elute the virus into suitable fluids.

Elution from Diatomaceous Earths

In order to investigate the possibility of elution, Superaid with adsorbed virus was shaken with a large number of solutions: alcohol diluted with saline to 1, 2, 5, 10, 20, 30, and 50%; alcohol diluted with phosphate buffers (pH 7.8 and 8.0) to 20 and 50%; phosphate buffers (pH 5.8, 6.2, 6.6, 7.0,

7.4, 7.8, and 8.0); glycerine undiluted and diluted in saline to 50, 30, and 10%; sodium citrate 2 and 1%; phenol 5, 3, and 1%; sodium hydroxide 4, 2, and 1%; dextrose 5 and 1%; urea 5 and 1%; glycine 5 and 1%; alanine 1%; and tyrodes solution. All failed to elute measurable amounts of virus, but disodium phosphate in concentrations ranging from molar to 1/10 molar and ammonia in concentrations from molar to 1/20 molar eluted some virus. Although the over-all yields were very low and they increased with increasing concentration they were never above 25% even with molar solutions. Protein-containing solutions such as normal horse serum, broth, and isinglass were more satisfactory. Experiments with these solutions are shown in Table V and indicate that the highest yield was obtained with 6% isinglass solution.

TABLE V

ELUTION OF INFLUENZA A VIRUS FROM DICALITE SUPERAID

Pool titre	Supernatant titre	Eluent	Eluate titre	% Over-all yield
512	64	100% broth	128	25
512	64	50% broth	96	18
512	64	25% broth	32	6
512	64	5% broth	<8	0
512	64	100% serum	128	25
512	64	50% serum	128	25
512	64	25% serum	128	25
512	64	5% serum	24	5
512	64	6% isinglass	192	38

Note: Over-all yield calculated by comparison of pool and eluate titres.

The isinglass solution was obtained from hake sounds, being prepared by our colleague Dr. Hill Bett. The highest concentration available was 6% and experiments were therefore carried out to determine at what strength most elution occurred. In one experiment, 5 cc. of isinglass solution varying in concentration from 0.0 to 6.0% were shaken for 10 min. at room temperature with 0.2 gm. of Superaid on which virus had been adsorbed. The results given in Table VI indicate that a maximum yield is obtained at about 1.0% isinglass.

In other experiments the yields remained constant above approximately 0.6% and were markedly reduced below this concentration. The constant maximum yield, however, varied with different experiments.

In the next series of experiments the various conditions that might possibly affect the yield were investigated. The virus from 5 cc. of allantoic fluid was adsorbed by shaking with 0.2 gm. of Superaid for five minutes at room temperature. Elution was carried out as already described at 0° C., 29° C., and 45° C. using 1.2% isinglass and shaking for 1, 5, 15, and 30 minutes. In one experiment an over-all yield of 50% was obtained at all these temperatures

TABLE VI

ELUTION OF INFLUENZA A VIRUS FROM DICALITE SUPERAID BY ISINGLASS SOLUTION

Pool titre	Supernatant titre	Isinglass concentration, %	Eluate titre	% Over-all yield
512	8	6.0	256	50
512	8	3.6	256	50
512	8	1.2	256	50
512	8	0.36	128	25
512	8	0.24	128	25
512	8	0.12	96	19
512	8	0.06	48	9
512	8	0.012	<8	0
512	8	0.00	<8	0

Note: Over-all yield calculated as in Table V.

and times. Other experiments have given comparable results. Thus, within the limits practicable for viruses, the elution would seem to be largely independent of time or temperature.

Many experiments have been carried out in attempts to raise the over-all yield above the 50%, which seems to be the maximum average. Modification of the pH of the fluid before adsorption to pH 6, 7, 8, and 9 with hydrochloric acid and then elution with isinglass solution at pH 7, 8, and 9.6 gave no better results. Superaid previously used for adsorption and elution was also tried but such treated material failed to adsorb virus from fresh fluid.

In the preceding experiments, the volume of eluting fluid was equal to that of the allantoic fluid from which the virus had been derived. In other experiments, in which the volume was reduced to 1/5th or 1/10th, the over-all yield was the same, the actual titres of the eluates being correspondingly higher.

Although most attention has been paid to elution from Superaid, elution from Filter-Cel and other diatomaceous earths by isinglass solution would seem to be equally efficient.

Elution from Clays and Charcoals

One preliminary experiment in which the virus from 5 cc. of allantoic fluid at pH 7.0 and pH 8.6 was adsorbed by shaking with 0.2 gm. of the various adsorbents at room temperature for 15 min. was carried out. The supernatant fluid was removed after centrifugation and replaced by 1 cc. of a 1.2% isinglass solution. In this way, if complete elution was attained, the virus should be concentrated five times. After further shaking at room temperature for 15 min. the tubes were again centrifuged and the eluates, supernatants, and pool samples titrated.

The results given in Table VII indicate that some virus is liberated from Baker's bone charcoal, Norrit A charcoal, kaolins, and Lloyd's reagent. Since the adsorptive power of these substances is in most cases much greater

TABLE VII

ELUTION OF ADSORBED INFLUENZA A VIRUS FROM CHARCOALS AND CLAYS BY ONE-FIFTH VOLUME OF 1.2% ISINGLASS

Adsorbent	pH 7.0				pH 8.6			
	Pool titre	Super titre	Eluate titre	% Over-all yield	Pool titre	Super titre	Eluate titre	% Over-all yield
Charcoals								
Nuchar	512	<8	<40	0	512	16	<40	0
Norrit A	512	16	640	25	512	<8	320	12
Bone	512	64	80	3	512	64	40	2
Decolorizing	512	12	<40	0	512	<8	<40	0
Clays								
Kaolin (Merck)	512	8	480	19	512	16	960	37
Kaolin (BDH)	512	<8	160	7	512	<8	240	9
Fuller's earth	512	<8	<40	0	512	<8	<40	0
Lloyd's reagent	512	<8	240	9	512	24	160	7

Note: Over-all yield calculated as in Table V.

than that of the diatomaceous earths, it is to be expected that elution will be more difficult. The failure to release virus by treatment with isinglass solutions does not necessarily mean, therefore, that inactivation has occurred. It is quite possible that variation of the concentration and the pH of the isinglass might increase the yield of virus from these substances but this must be left to further study.

Adsorption and Elution of Influenza B Virus

For convenience, the experiments already reported have been carried out mainly with influenza A virus. One experiment, however, carried out with Dicalite Superaid and three pools of allantoic fluid infected with influenza B virus indicated that under the conditions necessary for maximum adsorption and elution of A virus, the over-all yield with B virus is much the same. This would suggest that there is little if any difference in the adsorptive characteristics of the two viruses.

Poisoning

While in general, adsorption of the virus by Superaid is reasonably complete, it may occasionally fail altogether or be minimal in amount. Investigation showed that this might occur if traces of mineral oil (liquid paraffin) were present in the allantoic fluid. The addition of formalin 1/500 or merthiolate 1/20,000 did not prevent adsorption or elution, nor did contamination of the

allantoic fluid with egg yolk or egg albumin. Other sources of poisoning have not been investigated, although sterilization in the autoclave, or by dry heat in an oven at 170° C., does not harm the Superaid in anyway.

Immunity Experiments

In order to show that influenza A virus after adsorption and elution was still antigenic, the virus in 100 cc. quantities of allantoic fluid was adsorbed on 4.0 gm. of Superaid at room temperature for one hour, with frequent shaking. The supernatant was removed after centrifugation and 100 cc. of 1/500 formalin in saline added. After shaking, the mixture was left in the refrigerator for 18 hr. It was then centrifuged and the supernatant removed. Ten cc. of 0.6% isinglass were added and elution carried out for 90 min. at room temperature. The red cell titre of the original fluid was 500 and of the eluate 2560. The eluate was used for the immunization of mice, dilutions of 1/100 in saline being employed. Two 0.5 cc. amounts were given intraperitoneally seven days apart to groups of eight mice. Seven days later they were given living PR8 virus intranasally. The virus suspension employed was titrated by making 10-fold dilutions in tryptic digest broth and inoculating groups of six mice intranasally. From the number of deaths at each dilution, the dilution that would give 50% mortality (LD_{50}) could be calculated by the method of Reed and Muench (11). One death occurred in each group receiving 11,200 LD_{50}'s, another in the group receiving 5600 LD_{50}'s, whereas seven out of eight, and eight out of eight of the control mice died. Other experiments giving somewhat similar results have been carried out.

Discussion

Although the loss of virus in some types of filtration has been considered as due to adsorption by the filter, relatively little work has been carried out on the actual mechanism of adsorption of viruses. Reports in the literature are largely contradictory but under suitable conditions viruses such as vaccinia (6, 7, 13, 14), fowl pox (5), sheep pox (12), Rous sarcoma (8), as well as numerous bacteriophages (1, 2, 3, 5, 9, 10) can be adsorbed without inactivation by inert substances such as kaolin, kieselguhr, charcoal, and alumina gel. From the experiments carried out with other materials it would appear that the grade (which depends on previous treatment) of the adsorbent is very important. This may possibly account for some of the discrepancies in the work of others. Certainly with a suitable grade of adsorbent the adsorption of influenza virus from allantoic fluid is a reasonably consistent phenomenon. Experiments have been given showing that a portion of the adsorbed virus can be eluted by treatment with protein solutions such as isinglass. Since adsorptive forces decrease as polarity of solvent increases and are therefore lowest in water solutions it is improbable that this is a true elution but rather an elution by replacement. Nevertheless, there is no doubt that material capable of agglutinating red cells and immunizing mice against living influenza virus can be obtained in this way.

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NUTRITIONAL DISEASE AFFECTING CANADIAN TROOPS HELD PRISONER OF WAR BY THE JAPANESE[1]

By J. N. Crawford,[2] and J. A. G. Reid[3]

Abstract

The authors present observations on nutritional disturbances that they made on Canadian troops over a period of 44 months, during which time they were prisoners of war in the hands of the Japanese. The presentation is made against a background of dietary intake, energy output, and intercurrent infection. The chronological sequence of the development of signs and symptoms is shown. The impression of the authors as to the specific deficiency involved in each of these is indicated, where such an impression exists. The effect of dietary deficiency upon the various systems is shown, and a composite picture of the deficiency syndrome is presented, with remarks upon various aspects of it. The response to minimal treatment is described.

A. Introduction

On Dec. 25, 1941, 1686 Canadian soldiers were captured in Hong Kong by the Japanese, and were held prisoners of war, either in Hong Kong or the Japanese Islands, until September, 1945. This article is a general description of the nutritional disturbances that affected this group during the period of internment.

The discussion may be outlined in two phases:

I. The First Year, 1942

At this time, all the troops under consideration were confined in the Hong Kong area. This was a period of rapid deterioration of health associated mainly with:

(*a*) A diet grossly deficient in animal protein, animal fat, and caloric content, and with the B-complex exhibiting the most spectacular inadequacy with respect to vitamins. The change from the Canadian army rations to the prisoner regime was very abrupt.

(*b*) Severe intercurrent infections of which the outstanding examples were dysentery, diphtheria, and malaria, and for which facilities for treatment were markedly inadequate.

(*c*) Exhausting physical labour on work parties.

The result during this year, 1942, was widespread emaciation and the development of deficiency syndromes, mainly due to vitamin B complex deficiency and to a lesser extent to vitamin A deficiency. It was of interest

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to observe that there was a total lack, clinically, of vitamin C deficiency in spite of a diet that would be regarded, generally, as very inadequate in this vitamin.

II. The Subsequent Years, 1943-44-45

During this time, at varying intervals, drafts of prisoners were removed to Japan, until by the war's end the majority had left Hong Kong. Despite the geographical difference the general picture was fairly uniform. This period was essentially one of a partially successful struggle to improve the state of health in face of:

(*a*) A diet somewhat more varied, though often no higher calorically than in 1942.

(*b*) Some adjustment of the group to the inadequate diet, and a tendency to reach a plateau of a lowered state of health.

(*c*) A still deficient, though somewhat improved supply of medicines.

(*d*) The continuance of intercurrent infection although the types were now of a somewhat different character, with an important place being taken by chronic enteritis, infectious hepatitis, short-term fevers, influenza and pneumonia, tuberculosis, and skin infections.

(*e*) Work parties, which in Hong Kong were less arduous, while in Japan they continued to be severe.

It is useful to keep in mind these two broad periods, that is, 1942, and the subsequent years, while we discuss the background of diet, energy output, and intercurrent infections and the foreground of nutritional disturbance with specific deficiency syndromes.

It may be said that 1415 individuals survived internment and returned to Canada. After examination they were all placed on intensive dietary and vitamin therapy, efforts were begun to combat existing disease conditions and their reaction to treatment observed. Various groups were specially studied and certain figures referred to in this paper are derived from one of these groups, which included 521 men who, while living in one area of Canada after their return, during internment had been scattered throughout all the camps in Hong Kong and Japan and thus are a fair sample of the whole. It is hoped that in the future follow-up reports on nutritional recovery and on special problems mentioned here may be undertaken profitably.

B. The Background

I. Diet

Table I shows the average daily diet of prisoners of war in the Hong Kong area during the whole period of internment.

It should be emphasized that even when the protein values, as shown, would appear to approach physiological levels, the supply from animal sources was always very low. Soya beans provided the best grade of vegetable protein but were also present in small quantities.

TABLE I

AVERAGE DAILY DIET OF CANADIAN PRISONERS OF WAR IN THE HONG KONG AREA

PERIOD	JAPANESE ISSUE, gm.											SUPPLIED FROM OTHER SOURCES, gm.															DAILY TOTAL, gm.			
	POLISHED RICE	WHITE FLOUR	MEAT	FRESH FISH	SALT FISH	SOYA BEAN	MIXED VEGETABLE	COOKING OIL	WHITE SUGAR	DRIED FRUIT	SALT	TINNED BEEF	M.& V. RATION	FRESH PORK	SOYA BEAN	ATTA	WHOLE WHEAT	BRAN	COCOA	GHI	BEEF DRIPPING	COOKING OIL	PEANUT BUTTER	FRESH VEGETABLE	DRIED FRUIT	WHITE SUGAR	BROWN SUGAR	CARBOHYDRATE	PROTEIN	FAT	CALORIES
1942 Jan.	226.5		6.4				27.1				0.4																	189.7	21.2	3.1	898
Feb.	255.2	158.2	32.3			31.2	59.0		68.0		6.2																	403.0	52.4	17.6	2010
Mar.	310.4	161.6	80.8			7.9	112.3		40.0																			413.1	58.0	22.0	2138
Apr.	305.3	318.3	72.0			0.9	96.7	2.3	22.4	17.0	7.7																	509.1	73.9	23.4	2613
May	278.4	221.7	58.7				229.9	0.3	17.3	5.4	7.4																	485.4	72.3	19.2	2468
June	168.3	256.0	85.9				273.8	0.3	16.2	3.1	7.4																	368.9	61.3	21.9	1895
July	232.2	280.6	66.1				221.0	0.3	17.9	14.2	6.5																	421.6	65.1	19.7	2151
Aug.	206.0	269.8		36.9			160.7	0.6	18.4		4.5																	411.4	51.0	5.7	1981
Sept.	266.0	263.8		36.9			153.9	0.3	17.4		4.5																	431.0	58.2	6.3	2068
Oct.	360.0	277.2		34.9		6.0	227.4	13.9	7.2											28.3								511.4	68.3	33.1	2753
Nov.	381.2	141.7		39.4		2.6	280.7	16.4	5.3		3.9	13.6								28.3					11.6	6.5		440.2	57.5	55.0	2430
Dec.	400.0	163.5		50.2		5.1	289.2	23.6	4.6		3.9	54.4	76.8						4.0	28.3					12.5	24.1		501.9	79.9	59.2	2980
1943 Jan.	427.1	169.8		38.3		2.8	254.3	19.6	4.7		3.9	66.9	49.0						0.9	7.0					4.5	7.1		526.9	72.3	42.6	2766
Feb.	440.0	189.1		45.1		3.1	198.0	18.4	3.0		4.5	46.5	27.5			21.8			1.1	1.7					0.9	14.5		547.0	83.1	37.3	2946
Mar.	430.0	169.8		49.6		0.3	189.4	22.0	6.1		3.9	32.4	32.3			40.0			2.3	8.5					4.3	79.4		582.5	74.6	38.7	3067
Apr.	452.6	185.6		57.6		2.8	190.0	17.3	6.4		4.8	42.5	30.1			50.0			1.1						3.7	18.7		575.3	82.8	31.7	2989
May	410.0	141.7		46.8		4.8	200.2	21.4	5.0		3.9	39.1	28.6			56.7			2.3	5.7					3.7	46.2		542.1	73.4	36.9	2864
June	384.0	104.0		53.6		3.7	230.8	21.3	3.8		4.2	20.1	26.9			47.0			1.4						3.1	3.1		442.2	62.8	29.1	2332
July	371.6	114.7		51.5		4.0	190.2	16.0	5.0		5.5	14.5	15.5	0.75		42.8			0.9						4.0	23.9		452.4	59.2	22.9	2326
Aug.	380.0	118.1		54.1		2.8	199.0	14.0	5.0		4.5	16.4	13.3			42.8			1.1						4.0	39.1		477.9	62.2	21.5	2412
Sept.	384.0	118.1		55.3		3.0	252.0	27.6	5.0		5.0	24.2	32.3			48.5			1.4						4.1	24.6		474.1	56.4	36.2	2548
Oct.	384.0	118.7		58.0		3.0	232.0	23.4	5.0		5.0	24.2	32.3	1.46		48.5			1.4						4.1	17.3		466.1	66.6	33.0	2487
Nov.	415.0	75.0		64.8			233.0	19.0	4.0		4.5	10.5	20.1			56.6			1.4						2.0	10.0		510.7	63.9	23.9	2566
Dec.	475.0	61.5		61.9			408.0	20.0	5.0		5.0	10.5	20.1	13.1		56.6			1.4						2.0			554.3	67.8	28.0	2804
1944 Jan.	473.0	104.0		67.4			301.6	20.0	5.0		5.0	8.1	16.2	3.4		28.3			1.2									493.7	68.5	24.5	2546
Feb.	600.0			76.1		3.0	367.4	21.6	5.0		5.0	16.2	32.4	2.0		28.3			1.1							5.0		533.6	65.7	28.8	2729
Mar.	430.0			64.3		3.0	377.4	18.4	5.0		5.0	8.1	16.2	10.1		28.3			2.2							5.0		382.5	50.0	24.6	2006
Apr.	475.0			62.7		3.0	507.2	17.3	5.0		5.0	16.2	32.4	23.7	9.7	28.3		17.7	2.2				1.1			5.0	2.9	447.6	63.6	32.6	2775
May	463.0			86.3		3.0	388.9	16.8	5.0		5.0	13.5	18.1	14.7	6.0			1.8	1.1				1.0			4.5	2.0	406.6	51.6	27.2	2173
June	477.0			80.9		3.0	434.0	25.9	5.0		5.0			3.9	32.7			20.0			1.1					2.2	5.5	425.8	62.2	32.7	2327
July	472.8			68.7		2.9	269.3	23.8	4.2		4.8				44.0			25.7			3.4		1.8	23.8			3.9	412.0	63.8	36.5	2432
Aug.	462.5			72.0		2.5	363.5	11.0	4.2		4.0				25.4		1.1	19.7			2.7			35.1			5.3	412.8	53.8	21.0	2071
Sept.	475.1				43.7	3.8	323.5	32.5	7.0		4.8			7.7	34.1		3.5	14.8						18.4				413.0	58.1	44.8	2350
Oct.	466.6				32.8	2.9	303.8	18.4	5.2		4.2			4.3	35.3									36.3				395.4	47.6	26.8	2069
Nov.	482.2				42.5	3.1	320.6	24.2	5.1		4.8				31.6									25.9				414.2	60.6	35.7	2278
Dec.	475.3				44.1	3.1	356.7	26.7	5.0		5.0			5.9	33.7			21.2		3.3	3.5			20.4			5.5	416.1	60.0	46.8	2411
1945 Jan.	457.4				33.9	2.7	226.0	19.0	5.1		4.1													22.6				387.1	40.0	39.4	1921
Feb.	486.6				4.6	2.9	286.9	29.5	5.0		3.7							22.3						16.4			9.0	419.3	58.8	28.5	2147
Mar.	490.3					30.2	279.3	26.3	5.6		5.0													12.7				422.1	47.4	30.7	2211
Apr.	481.1					29.2	161.8	22.2	5.0		5.2			6.8				24.8						37.6			16.2	425.2	46.7	29.1	2209
May	481.4		6.4			30.1	370.3	36.6	5.2		6.5													50.9				420.4	49.0	40.8	2306
June	516.8		31.0			3.6	992.0	8.7	7.3		9.1													122.0				446.5	47.9	17.8	2197
July	462.3		31.5	10.6			384.9	12.7	7.8		8.4							23.1						186.9			25.7	407.0	58.2	27.4	2161

The food quantities shown represent the weight of food supplied to the cookhouse. No account has been taken of cooking loss or of inedible portion. The meat issue is whole carcass, including bone. The fish issue, about half the time, was so rotten as to be almost entirely inedible. Other items such as rice, which would normally be considered to be completely edible, usually contained significant adulteration with sand or quartz.

Thus the quantities of food nutritionally available to the individual are less than indicated in the table.

Commodities supplied are tabulated as Japanese issue and issue from other sources, the latter including three: the International Red Cross, which supplied bulk food in the autumn of 1942; a farm operated inside the camp by the prisoners themselves subsequent to 1942, which supplied a certain amount of fresh pork and vegetables; local purchases made unofficially in the 'black market'. This division is of interest to show the monotony of the diet from Japanese sources and the great improvement brought about by the additional food.

Food values have been calculated using as authority the Manual of Hygiene of the Indian Army, where are to be found many of the more bizarre types of food, such as atta, a flour of soft Indian wheat, and ghi, a butter made from the milk of the water buffalo. When a particular article of food was not shown in a food table, calculations have been made on the basis of a reasonable European equivalent.

Vegetable is shown, and calculated, as mixed vegetable. As supplied, this was mainly 3% carbohydrate vegetable with small amounts of 20% CHO vegetable. The food value of the total was calculated on the basis of average content, varying with changes in bulk composition.

Cooking oil was generally peanut oil, occasionally a bean oil of uncertain value or cocoanut oil.

With such limited materials at hand, monotony of diet was inevitable. A typical day's menu would be:

Breakfast—a porridge of rice, ground soya beans, and bran when available.

Dinner—rice and vegetable soup, with added meat or fish when available.

Supper—rice and vegetable soup.

If flour was supplied a sour-dough bread was produced, and the whole menu was varied within narrow limits according to available foodstuffs.

During the early months of internment the food was somewhat overcooked owing to fear of parasitic infection. This fault was later corrected. Alkalies were never used in cooking. It is hoped that it will be possible to complete a vitamin assay of this diet at a later date.

From Table I it is obvious that in the first nine months of 1942 the diet was one of about 2000 calories daily, markedly below the caloric requirements of the men at that time, with very little animal protein and animal fat, and very low total fats. During this period there became manifest rapid weight loss,

proceeding in many cases to gross emaciation, and deficiency syndromes appeared and increased rapidly in frequency and severity.

In the remainder of 1942 an abrupt caloric rise to 2700 to 3000 calories daily, followed the receipt of Red Cross food supplies in October, 1942, an effect that was felt by the whole group of prisoners. One can note the attempt to maintain this level by the conservation of these supplies for the gradually decreasing Hong Kong population through the spring of 1944, at which time this original Red Cross shipment was finally exhausted. The second drop in caloric value at this time was again associated with a decline in the general state of health but the manifestations of this differed from those of 1942 (*vide infra*). In Hong Kong also, the return of meat to the diet, following the collapse of Germany in May, 1945, had a remarkable effect in raising morale.

In January, 1943, the first draft of Canadians, some 660 men in the relatively better states of physical health, were transferred to Japan, 500 of these being settled in the Tokyo area. Table II correlates the diet of the latter group with that of the Hong Kong group. The peak dietary period of this group obtained from January, 1943, to June, 1943, and the example 'June 1943' is one showing the zenith of this period. Rations were subsequently steadily decreased to the second example in 'November 1943' and subsequent periods in 1944 and 1945 were never more than slightly improved to this latter example. This is reflected in weight graphs of the Tokyo group (Fig. 1).

Here, again, we note that over most of the Japanese stay the caloric intake was much below our usual requirements, animal protein was excessively low

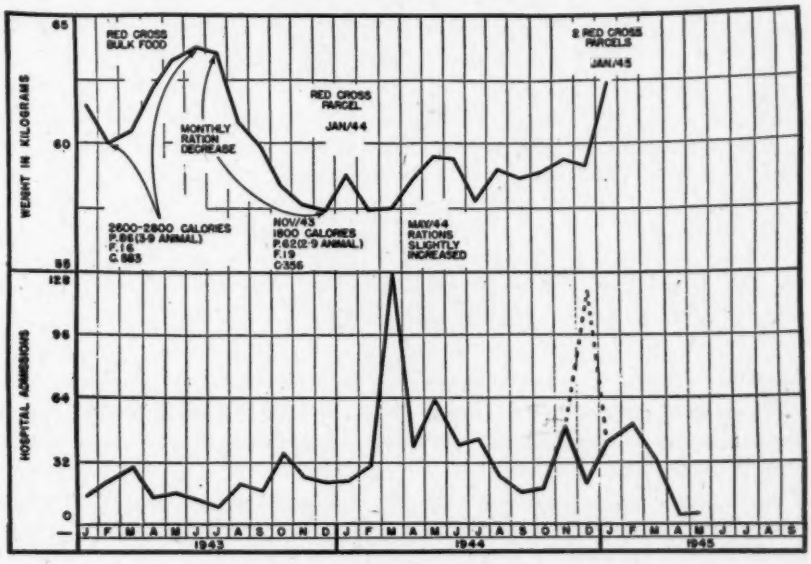

FIG. 1

TABLE II

DIET IN A PRISON CAMP IN JAPAN, DAILY AVERAGE/MAN

June, 1943		November, 1943	
Total weight of food	1.4 kgm.	Total weight of food	1.4 kgm.
Variety in % total weight:		Variety in % total weight:	
Rice	23.5	Rice	3.9
Barley	23.2	Barley	6.1
Flour	0.23	Maize	10.0
Macaroni	0.28	Bread	3.2
Bread	1.8	Meat	0.61
Meat	0.97	Fish	1.0
Fish	1.3	Soy beans	6.3
Red beans	0.41	Soy bean derivative	1.6
Soy beans	0.41	Soy sauce	3.2
Soy bean derivative	1.4	Oil	0.47
Oil	0.15	Sugar	0.16
Sugar	0.14	Salt	0.39
Salt	0.25	Cabbage	28.3
Cabbage	19.2	Kabo*	0.55
Lettuce	4.9	Daikon**	7.6
Kabo*	4.1	Irish potato	24.4
Daikon**	3.0	String beans	0.71
Irish potato	7.5	Bean sprouts	1.0
Sweet potato	0.97	Onions	0.21
Spinach	0.41		
Burdock	0.41	Grain	19.6
Yams	0.55		
Green tops	0.28	Mixed vegetable	67.6
Onions	4.8		
		Food value in gm.:	
Grain	46.7	Carbohydrate	356
		Protein	62 (2.9 animal)
Mixed vegetable	47.6	Fat	19
Food value in gm.:			
Carbohydrate	583	Caloric value	1840
Protein	86 (3.9 animal)		
Fat	16		
Caloric value	2800		

* *White turnip.*
** *White radish.*

and the total fats were in very small amounts. However, it is also notable that the variety of vegetable and grain was always greater than in the early Hong Kong period.

II. Energy Output

No critical study of energy output can be presented here, as no such study was made during internment. Certain factors bearing on this subject are, however, obvious.

Work parties began in April, 1942. The work parties left camp at or before dawn, were given their midday meal on the job, and returned to camp at or after dark. The men were constructing an airport and the type of work was hard, pick-and-shovel labour. The work party was a rotating duty.

At first an individual man went out one day in three. Soon more men were required by the Japanese. Coincident with the increased requirements an increase in the sickness rate occurred and was aggravated by the constant energy drain. By June, 1942, it was difficult to find enough of the fitter men in camp to fill the required quota, and these men were working four days out of five, with the sicker individuals remaining in camp. By September, 1942, the Japanese were imposing a quota on fitter and sicker men alike, and during this period many men whom the medical officers felt were dangerously ill were forced to work.

In the spring of 1942 a certain amount of softball and volley ball was played on 'days off'. The more violent forms of sport were actively discouraged by the Canadian medical authorities. However, the question of morale had to be weighed against that of exhaustion and it did not seem wise to prohibit sports altogether. There was never at any time any compulsion to play games, personal inclination being the only determining factor. Later in 1942 the Japanese did enforce P.T. as a method of combatting the increasing deficiency diseases, but this was always performed under the direction of Allied officers and was, in substance, innocuous. Gradually, the number who played games was confined almost entirely to officers who did not go on work parties.

A group of 'amputees' exhibited an interesting comparison to the ordinary population of the camp. These men did not go on work parties, nor did they indulge in sports, but received the same diet as the remainder of the camp. This group did not suffer from nutritional disturbance until late in internment, nor did they ever suffer to as great a degree as the general population. When, finally, they did show some signs of deficiency it was of the type that we had come to associate with ariboflavinosis.

In Hong Kong after January, 1943, work parties ceased for a few months as a result of the great sickness rate and the removal of most of the fitter men to Japan. In Hong Kong at that time better feeding obtained and the general level of health improved. Work parties began again in April, 1943, but were never so arduous as in 1942.

However, in Japan, the various groups, from the time of their arrival there, always performed very exhausting work, mainly in the line of shipbuilding, stevedoring, or mining, and their energy output was always very high. Moreover, these groups were always issued rations at the rate of a full ration for every working man, a two-thirds ration for men sick in quarters, and one-half ration for hospital cases. This often provided a serious problem, necessitating the working of chronically ill men to keep the camp ration level above that of stark starvation. The men always desired that all rations be equally divided among them and this was carried out despite many difficulties with the Japanese who wanted to impose the reduced ration on the ill men. The reduced rations, in face of the ever-present malnutrition, would, of course, have been below the level necessary to maintain life.

III. Intercurrent Infections

The contribution of intercurrent infections to the general picture of deficiency syndromes cannot be overemphasized. In 1942 the outstanding examples were dysentery, diphtheria, and malaria or short-term fevers such as dengue.

(*a*) *Dysentery*

Lacking a microscope, the diagnosis of dysentery was made on clinical grounds, the main criteria being blood and mucus in the stools. A division into bacillary and amoebic types was made, tentatively, according to the mode of onset, course, and response to the very small doses of Japanese sulphapyridine available through 'black market' sources. More certain diagnoses were later available when a microscope was procured, but always one of the most interesting and remarkable features of the disease was the response of the acutely ill bacillary type to such homeopathic doses of sulphapyridine as 0.5 gm. every four hours for four doses.

Internment had barely begun when the problem of dysentery became acute. The conditions of starvation and overcrowding were ideal for the spread of an epidemic. No accurate figures are available to show the actual incidence of the disease at any given time. Many, if not most of the chronic cases were treated outside of hospital and are unaccounted for, but the admissions to hospital per month ranged from 8 to 11% of the camp force of about 1500 men throughout 1942.

In the second phase of 1943-44-45, the incidence of acute cases gradually decreased, until it had practically disappeared in Hong Kong by August, 1944. In Japan, from available records, the acute cases had almost entirely ceased by late 1943. However, in both areas, the sequela of chronic, recurrent enteritis was always very widespread and debilitating.

In all, 58.3% of the force gives a history of having suffered dysentery, and most of these cases occurred during the first year of internment.

Dysentery was perhaps the most important forerunner of nutritional disease. Those rare individuals who escaped some major manifestion of nutritional disturbance are almost exclusively to be found among those who escaped frank dysentery. The onset of dysentery in an individual during the early months of 1942 was usually a guarantee that this patient would later develop a deficiency syndrome.

The question of chronic enteritis is a vexed one. At times it was difficult to decide whether this was the cause or effect of nutritional disturbance. It was frequently a sequela of dysentery, but also occurred separately. Further, a suspected and complicating picture of widely varied pathogenic parasitic infestation, including an ascaris infestation rate of 34%, has been confirmed since return to Canada.

However, the importance of the factor of chronic enteritis can be gauged from the results of stool examinations on 458 men of the Tokyo group in June,

1944, which disclosed, in the gross, that 12% were passing liquid diarrhoeal stools, and 35% were passing undigested food per rectum.

(*b*) *Diphtheria*

Diphtheria, as a contributing factor to the breakdown of health, was confined to the first phase of internment. The first case was seen on Aug. 7, 1942, and the disease quickly assumed epidemic proportions. In six months 459 cases developed with the following incidence: August, 12; September, 67; October, 248; November, 106; December, 20; and January, 1943, 6. A very few sporadic cases occurred subsequently until the spring of 1943. The flare-up of the epidemic was markedly aided by the fact that the camp was moved from the Island of Hong Kong to the mainland on Sept. 27, 1942, and forced by the Japanese to carry active cases in conditions of unbelievable overcrowding. At this period our captors refused to countenance the diagnosis of diphtheria and would make no antiserum available.

Of the earliest cases, 101 received no anti-diphtheritic serum and of these 38, or 37.6%, died. The remainder of the cases received some specific treatment, the usual dosage being 1500 to 3000 units. Of these cases, 16 or 4.5% died, and almost all the fatal cases were complicated with acute dysentery, the two forming a very lethal combination.

The minimal amount of specific treatment available saved life, but, as would be expected, a large number developed paralyses in the course of their convalescence. This was coincident with the period when avitaminosis was at its worst with its own quota of peripheral neuritides, thus often posing a difficult aetiological question.

Although diphtheria killed 54 men, we feel that, paradoxically, it saved a great many lives. Routine pharyngeal swabs of the camp population began in October, 1942, and revealed a great many diphtheria carriers. These were isolated, and forbidden to go on work parties by the Japanese who had a great personal fear of this disease. These men continued on the usual diet but did no work, and thus soon exhibited a universal weight gain and improvement in their general state of health.

(*c*) *Malaria and Short-term Fevers*

Malaria, dengue, and short-term fevers of uncertain aetiology were widespread in 1942, involving most members of the camp population. With the consequent excessive utilization of calories, imposition of anorexia, and general debilitating effect, they were a potent factor in nutritional disturbances. Of the force, 41% had frank malaria during internment.

In the subsequent years, 1943-44-45, the character of intercurrent infections was somewhat different to that described above. Chronic enteritis, as pointed out before, continued to be a potent debilitating factor in both the Hong Kong and Japanese groups. In Hong Kong, malaria, short-term fevers, and infectious hepatitis were the most important additional infections. In the Japanese groups, whose total number became larger and larger during this period, other disease syndromes became prominent. Malaria became relatively insigni-

ficant, but short-term fevers in the summers, influenza, pleurisy, and pneumonia in the winters, and infectious hepatitis and tuberculosis throughout the year, were major problems. A general statement of the numbers affected by these disease groups can be gained from Fig. 2 (*vide infra*), which is taken from the 500 man Tokyo group, and is fairly comparable to all Japanese camps.

C. The Foreground of Nutritional Disturbance

Most of the specific deficiency pictures to be dealt with in this section were concerned with an insufficient supply of the vitamin B complex to body cells. The terms beri beri and pellagra will not be used in this discussion, and this omission is not unintentional. In our experience with avitaminosis we learned early that the cases were rare, indeed, that could be labelled as clear-cut beri beri or pellagra. In some cases, the generally accepted, particular manifestations of lack of one or other of the factors of the B-complex overshadowed that of other factors, but in most cases the picture was so variable, not only from individual to individual, but in one person at different times, that we classified them only as avitaminosis-B with a qualifying reference to presenting parts of the syndrome. Deficiency defects due to lack of vitamin A also played a definite part.

Altogether 100% of those interned suffered from some nutritional disturbance, 95% showing major manifestations such as neurological involvement or oedema and 5% minor lesions of the skin or mucous membranes.

I. Weight Loss

The immediate effect on the prisoners of the factors indicated in the 'Background' was a widespread loss of weight. In the first four months of 1942 the average weight loss was 15.4%.

In the study of any individual case it was, of course, extremely important to correlate weight with other aspects of the man's condition, and without such correlation the weight was not a reliable index of his state of nutrition. For example, an attack of dysentery might produce a decrease in weight of 10 to 15 lb. in a few days, following which the same individual might gain 15 to 20 lb. in the next several days. The first drop was mainly a reflection of dehydration, and in the gaining phase, oedema of tissue would become manifest.

However, the over-all picture of weight, elaborated as the average of any considerable, unselected group of prisoners, was an excellent indication of the trend of general nutrition. Such mean curves always paralleled the amount of food available.

Fig. 1 shows the average weight of the Tokyo group of 500 men through 1943-44. At the end of 1944, large sections of this group began to be scattered in other camps and the weights for 1945 are not of a comparable sample. They are, therefore, not included in this graph. There was, however, no remarkable change in the weight trend during 1945.

General indications of the food level are annotated. This curve clearly indicates the period of relatively good feeding, viz.; January, 1943, to June, 1943. It further reflects the continual, monthly ration decrease from July,

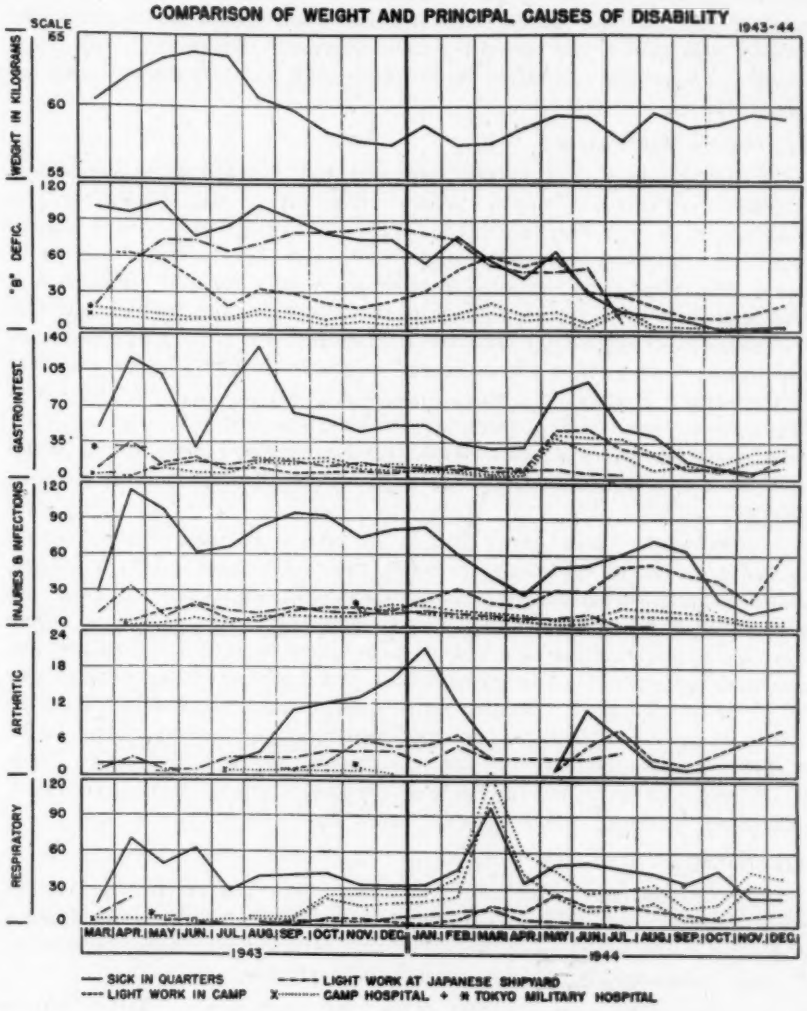

FIG. 2

1943, to December, 1943. Also it marks the outstanding effect on a group of men of the small addition of Red Cross food parcels, when the said group has reached a low plateau of more or less precarious nutritional equilibrium.

Fig. 1 includes a graph reflecting the hospital admissions of the group during the same period. This clearly presents the increase in serious morbidity in the winter of 1943-44, as a result of the partial starvation of the previous six months. The dotted rise noted in December, 1944, is factitious, as this was due to a group of chronically ill men removed to an outside rest camp by the anxious Japanese as the war drew to its obvious conclusion. This group would not have been admitted to hospital under the conditions obtaining previously.

II. Urinary Disturbances

The first syndrome that was observed, and that was thought to be due to a nutritional disturbance, was a marked irritability of the bladder and inefficiency of the urethral sphincter. Within a week of the abrupt change from Canadian Army rations to a ration consisting, at that time, of a cupful of rice and a bowl of watery soup twice daily, most individuals began to pass large quantities of very pale urine throughout the 24 hr. The night volume was considerably larger than the day volume, reflecting the climatic temperature drop at dark. Micturition occurred very frequently and rapidly assumed a 30 to 60 min. periodicity at night, somewhat longer by day. Within two to three weeks great urgency appeared and excessive dribbling was common. These conditions were almost universal through 1942 and 1943, though in the Japanese group this gradually became less severe in the last two years of internment.

Throughout the whole period 1942-45 the average individual passed 6 to 8 litres of urine daily. This was, of course, due to the type of diet, consisting always of grain cooked in water, and soups. The urgency, frequency, and lack of sphincter control, while almost universal, were definitely more pronounced in those cases that had developed gross neurological disturbances, and these symptoms seemed to be linked to a combined low-protein intake and neurological change. On the rare days when meat was issued in quantity in 1942, there would be widespread relief during the subsequent night. Later in 1943-45, when this urinary state was chronic, the receipt of a Red Cross food parcel, containing several meals of meat and cheese, always gave rise to improvement, though it was less spectacular than that described above.

III. Oedema

Oedema and paraesthesia (see IV) were the next manifestations of avitaminosis observed, and began to occur in March, 1942. In this month 44 cases of this type were seen, and, of these, the presenting complaint was oedema in 17 cases, paraesthesia in 11 cases, and both in 16 cases.

The initial oedema was confined to the lower extremities. Within two to three weeks it was appearing in the face and hands, and by May, 1942, ascites was not uncommon.

The onset of oedema at this time was heralded by a period of oliguria of one to seven days' duration, and by a rapid increase in weight. Generally, the weight gain was about 10 lb. before clinical oedema was evident. There

was no headache or backache, and the urine contained no abnormal amount of protein, as noted on boiling for five minutes.

In the beginning most cases responded to a sudden decrease in energy output. On bed rest and fluid restriction, diuresis usually occurred in 24 to 48 hr. and the oedema was relieved. However, these cases tended to relapse, and, as the condition became more widespread, the response to this type of treatment became discouraging.

In April, 1942, a small supply of thiamin hydrochloride became available for use. An intramuscular dose of 5 mgm. was tried and a very dramatic polyuria with decrease in oedema was produced. This was observed in many cases after one injection, in most after two or three. The diuresis was most marked nocturnally, probably being associated with a drop in the ambient temperature.

During most of 1942, oedema generally continued to respond well to the administration of thiamin, but, as time went on in this year, and oedema became more and more common, the amount of thiamin required in any individual case increased.

In May, 1942, two cases, both with ascites developing in the course of dysentery, failed to respond to thiamin in doses up to 20 to 30 mgm. intramuscularly, daily. At this time, there was a fortunate issue of whale meat, and thiamin was then withheld for two days, after which the two cases each received about $\frac{3}{4}$ lb. of this lean meat at one meal. Within eight hours an excellent diuresis occurred.

By the end of 1942, not only had the therapeutic dose of thiamin increased very greatly as noted above, but there were many cases of oedema on which it had no clinical effect, and much chronic oedema was in evidence. It was felt that these latter cases, and the two of ascites described above, were due primarily to hypoproteinaemia, rather than to a link in the physiological chain on which thiamin acted.

In this year the response of the oedematous cases to thiamin was at first dramatic and, later, very frequently satisfactory. Thus we felt that a direct relationship between lack of thiamin and fluid retention was established beyond doubt. We also felt that there was in evidence another type of oedema that seemed most probably due to the inadequate amounts of Grade A protein nutritionally available.

In the second phase, 1943-45, oedema was a prominent complaint at various periods and was always endemic. Throughout this time oedema, far more than any other symptom, paralleled very quickly any abrupt changes in either diet, energy output, or the loss of water and, particularly, metabolites, in excessive sweating. The response to thiamin during this period was very sluggish, although in about 50% of the cases it was a real one. However, it seemed more probable that such response was bound up with secondary improvements, as in appetite, resulting from the administration of thiamin, rather than in the direct way observed in the cases in early 1942. It was felt

that a general tendency to hypoproteinaemia existed throughout this period of the second phase.

In all, 79.6% of the prisoners exhibited oedema during the period of internment.

IV. Paraesthesia

Paraesthesia appeared concurrently with oedema in March, 1942. In the early stages, both in time and in the individual case, it consisted of (i) a subjective, tingling, 'pins-and-needles' sensation and (ii) a subjective numbness and objective hypoaesthesia. With progress, 'lightning' pains, hyperaesthesia to light touch and pin prick, and anaesthesia became very common.

The areas at first affected were usually the toes, progressing to the feet and legs. The hands became involved during this time. Later there was extension to the thighs and body and to the 'muzzle' area of the face, and in the trunk, well-marked, girdle somatic bands of involvement developed. The parts affected were usually fairly symmetrical.

The full-blown picture of this syndrome progressed steadily from its inception in March, 1942, until in the autumn of that year it was very common. It may be regarded at this period as the acute picture.

In 1943-45 it persisted more regularly as a chronic leftover from the earlier stage, and very gradually diminished in frequency and severity during this time.

In early 1942 a few of the first cases responded somewhat to either bed rest, thiamin hydrochloride, or both, but as the cases multiplied, the dose of thiamin offered, usually 5 mgm. intramuscularly, daily, gave no real help.

In the second phase, when some nicotinic acid was procured, doses of 50 to 100 mgm. daily for 7 to 14 days produced no clinical effect.

In Hong Kong in 1944, an injectable B-complex was obtained, containing riboflavin, thiamin, and niacin, and this produced a moderate improvement.

Slow, steady improvement occurred throughout 1943-44-45 in the Tokyo group, where a more varied diet with respect to grain and soya beans was in existence, and added treatment consisted of a reduction in energy output and doses of thiamin of 3 mgm., either daily, every third day, or every fifth day, for months at a time. Nicotinic acid and riboflavin were never available in Japan for treatment in therapeutic doses.

It thus appears that this syndrome responded mainly to increases in the whole B-complex, rather than to the specific portions thereof available to us for use. There was, however, some suggestion that riboflavin played a more important role than other factors.

V. 'Electric Feet'

(*a*) *Description*

'Electric feet' was a phrase coined at once by those who suffered from it, and the following syndrome was commonly referred to in this manner at all subsequent times. The name adequately described its chief symptom, viz.;

'lightning' pains of an 'electric shock-like' nature in the feet and legs. It has been referred to in most medical reports on prisoners of war in the Far East, and described under the name of 'Scott's Central Neuritis' in an old edition of Manson-Bahr. However, minor geographical differences appear to exist and this, with the widespread incidence, and grave effect on health and morale, justify a repetition of its description as seen among the Canadians.

The first indication of this syndrome was in April, 1942. At this time four men reported pain along the medial side of the sole of the foot. These men were all very weak, and it was suggested that pain was due to incipient pes planus, resulting from loss of muscle tonus. As the number of cases rapidly increased in epidemic proportions, and as other characteristics became apparent, the diagnosis of acute pes planus was quickly abandoned.

The pain was, at first, of a burning or 'toothache' quality, involving the soles of the feet, but it soon spread to the dorsum of the toes, and in the records at this time the descriptive term, posterior tibial paraesthesia, or P.T.P., was employed. Within two months the incidence of this complaint had greatly increased, and the pain had assumed an added 'lightning' quality, radiating up the legs. Severe progression of the syndrome occurred, usually, in cases with no oedema. The feet exhibited a periodic blushing, slight local swelling, and were very warm to objective examination. This appeared to be due to an arteriolar dilatation and was associated with an exacerbation of the discomfort.

The severity of the pains was subject to a definite periodicity, being greater in 90% of the cases at night, and in 10% during the daytime.

Some relief could at times be obtained by walking about, or massage of the legs (the feet being too painful to touch), which aided the blood flow through the part. Universally, improvement occurred by exposure of the feet to cold, which tended to decrease the blood flow and perhaps reduce sensory perceptions. For this reason, in late 1942, soaking of the feet in cold water was commonly resorted to and the actual prevention of this, among the suffering men, was very difficult, although it inevitably led to maceration and secondary infection of the skin. Thrombosis and gangrene of the toes and distal portion of the feet occurred in a number of cases, more frequently in those with water trauma, but also in cases in which this factor was absent.

Objective sensory changes included, early, a very marked hyperaesthesia of the feet, and patchy hyper- and hypoaesthesia of the legs. This typically progressed to a loss of the sensations of light and deep touch, and pain, in the feet and in this stage relief from the pain supervened. At this time, also, position sense and vibration sense were markedly impaired in the distal parts of the lower extremities.

When the syndrome was at its worst in the autumn of 1942, there were associated with it numerous other phenomena of nutritional disturbance, among which were tachycardia, photophobia with conjunctivitis, and profuse sweating. The combination of the red, painful feet with these observations

brought to mind the picture of acrodynia seen in children. Also observed at this time, more than at any other, were (1) the typical skin lesions, described under 'pellagra', on the exposed and friction surfaces of the body, (2) numbness and hypoaesthesia (occasionally hyperaesthesia) of segmental bands of the trunk, of the genitalia, of the 'muzzle' area of the face, and of the hands, (3) hypersalivation, (4) angular stomatitis, paranasal dermatitis, and corneal ulceration.

General constitutional deterioration was marked, due to the anorexia, prohibition of sleep, and the continual psychological drain associated with the very severe pain.

(*b*) *Treatment*

Temporary relief could be obtained in a number of ways. The application of cold to the involved extremities already has been mentioned. Partial relief, for one to two hours, also appeared to occur after heat was applied to the lumbar spine. The element of suggestion was not entirely ruled out in the latter cases. Morphia, as a final measure, gave help only in full doses.

In the fall of 1942, thiamin and nicotinic acid, both separately and combined, were used in an attempt to produce more lasting relief. It was our impression that thiamin, in doses of 5 to 20 mgm. intramuscularly, daily, had no effect whatsoever on the pain.

Nicotinic acid in doses of 20 mgm. daily, intramuscularly, produced a very definite result. The syndrome had developed through a hyperaesthetic stage to a hypoaesthetic stage to anaesthesia. At whatever stage the nicotinic acid was provided, this chain of steps was retraced. Thus, in many cases where the anaesthetic stage had not been reached, the immediate effect of the administration of nicotinic acid was to produce an exacerbation of the pain. In those where anaesthesia was present, sensory perceptions and, therefore, pain gradually returned. However, as treatment continued over months, pain again diminished as sensation progressed towards normalcy. The peripheral vasodilatation peculiar to nicotinic acid was, perhaps, a partial basis for the exacerbations of discomfort.

Thus, from a temporal association with 'skin pellagra', and from the clear response to nicotinic acid, we believe that the 'electric feet' syndrome is more closely associated with the 'pellagrinous' disturbance than with other types of the B-complex deficiency. However, it must be noted that this syndrome faded out of prominence in the first five months of 1943 in the Tokyo group, and was never an advancing syndrome in Japan. This was accomplished under the more varied and calorically improved diet shown in Table II, with no added nicotinic acid, but with small doses of thiamin available.

The syndrome appears to be a combination of a neurological and, either primarily or secondarily, a circulatory disorder, and probably has its basis in deficiencies of parts of the B-complex as yet not well understood, with perhaps other extraneous factors playing a part.

(*c*) *Effect of Previous Nutritional Habits*

In connection with the development of the syndrome of 'electric feet' a further interesting observation was made. It was early noted that 'electric feet' was responsible for a very major disability among one portion of the camp population, and left another portion almost unaffected. The camp population was of two types: (1) the one containing Canadians, British regulars, and Hong Kong citizens of European birth, who belonged to the Hong Kong Volunteer Defense Corps; (2) the other consisting of local residents of Hong Kong who had been born in or near the colony, many of whom were of mixed British–Portuguese–Chinese blood, and who had lived all their lives on substantially the same type of diet (although in larger quantities) as was available during internment.

In Group (1) the syndrome of 'electric feet' was very widespread and severe. In Group (2) it occurred with extreme rarity.

There was a great temptation to jump to the conclusion that the differentiating factor was one of accommodation to the available type of diet.

With the improvement of diet after December, 1942, and with the use of nicotinic acid in Hong Kong, the severe 'electric feet' syndrome largely disappeared. On several occasions in this second phase, both in Hong Kong and the Japanese Tokyo group, the diet again fell to very low levels, but each time the reduction was gradual and it is to be observed that at these episodes this type of food had been in force for two or three years.

Following certain of these reductions, particularly in Hong Kong, many of the earlier manifestations of avitaminosis recurred to a marked degree. These included oedema, paraesthesia, angular stomatitis, paranasal dermatitis, and glossitis. However, it was of great interest to note that the 'electric feet' did not reappear.

We feel that the rate of change from a good diet to a poor one, and the factor of accommodation to, and utilization of, the poor type of diet, should be borne in mind when making any attempt to assay the aetiology of the 'electric feet' syndrome.

VI. Neurological Disturbances

(*a*) Frequency and urgency of micturition, and deterioration of sphincter control, paraesthesia of the extremities, and the 'electric feet' syndrome, were early evidences of neurological involvement in the picture of nutritional disturbance.

Following rapidly on these, in the first phase, 1942, stretched a chain of signs and symptoms indicating further attack on the nervous system.

(*b*) Subjective numbness and hypoaesthesiae or anaesthesia of the upper and lower extremities, trunk, and 'muzzle' area of the face, have been mentioned above. This form of involvement was of the 'glove-and-stocking' type in the extremities, and progressed in an ascending fashion. In the lower extremities, in most cases, it did not extend beyond the mid-thigh, although numbness as high as the waist was not uncommon. In the upper extremities

the fingers were commonly involved but spread beyond the mid-forearm was rare. The trunk was typically affected in somatic, girdling bands, involving one or two dorsal roots in each area affected.

Prolonged treatment, with small doses of thiamin (average 6 mgm. weekly, intramuscularly) had a definite therapeutic effect. The addition of nicotinic acid, in the Hong Kong group, accelerated this effect, and the involvement reached a minimal stage (the persisting results usually being in the feet and toes) in both Hong Kong and Japanese groups by the middle of 1943, following the dietary improvement previously described.

Retrogression of these phenomena was always in a descending fashion.

After return to Canada, 84% of the repatriates gave a history of this neurological type of damage during internment, and it was still in evidence in 51% of them.

(*c*) The deep tendon reflexes were involved early in 1942. This effect was seen most commonly in the lower extremities, the patellar being more frequently attacked than the ankle jerk. The first change was hyperactivity, which progressed through hypoactivity to complete loss. Recovery occurred in response to thiamin and was in the reverse order.

Abnormality of these reflexes was, however, a very longstanding feature and persisted in a not inconsiderable number of cases throughout the whole of internment.

(*d*) Ataxia was a very common complaint. The full-blown cases walked with a wide-based, high-stepping, toe-slapping gait and were unable to maintain balance in the dark. Typical Rombergism was present.

(*e*) Abnormal calf tenderness had its onset in the early spring of 1942, and persisted, though very slowly diminishing, throughout internment. It was very common and was regarded as secondary to a peripheral neuritis.

(*f*) During October and November, 1942, four cases of acute mania were seen. All four cases were suffering from diarrhoea, and all four had very painful feet. One case had a typical pellagrinous dermatitis at the time of onset of the mania, and one case had suffered such a dermatitis one month previously. The remaining two had stomatitis and scrotal dermatitis (*vide infra*).

The onset of mania was abrupt, with a period of four to eight hours of abnormal behaviour, including excessive motor activity and bursts of incoherent conversation. One case had the delusion that he was a cat. Two cases developed convulsions of the grand-mal type. Following this initial phase the patients collapsed into a state of muttering delirium, punctuated by bouts of struggling and shouting.

All four cases received nicotinic acid intravenously, in doses of 100 mgm. This resulted in a prompt and dramatic improvement. The patients became quiet and then slept soundly. The following day they were rational, with an amnesic period for the episode of the acute mania. The diarrhoea and painful feet were unchanged.

VII. Lesions of Skin and Mucous Membranes

Abnormalities of the skin and mucous membrances appeared in May, 1942, and had their epidemic fling in the first year, although some appeared somewhat earlier than others, and some persisted in the chronic state throughout the second phase, 1943-45.

(*a*) *Stomatitis*

The first of these was a severe stomatitis involving 67% of the camp population. It produced a fiery red, shiny, smooth surface to the buccal, pharyngeal, and glossal mucous membranes. Hypersalivation was present and there was marked discomfort. Eating was painful. Repeated examinations failed to discover Vincent's organisms. Nicotinic acid was not available for treatment and thiamin was quite without effect.

Treatment consisted of mouth washes with a weak solution of potassium permanganate. Toward the end of August, 1942, the involvement of the buccal and pharyngeal areas began to subside and by mid-October had completely disappeared, although the diet during this whole time had remained essentially unchanged.

The tongue, however, remained smooth, shiny, and red and progressed to the lesion described below (*g*).

(*b*) *Scrotal Dermatitis*

Scrotal dermatitis appeared at the same time as the stomatitis but persisted longer. It occurred, in all, in about 50% of the camp population. It decreased markedly by the end of 1942, but sporadic cases presented from time to time until the end of internment.

In the beginning the skin of scrotum assumed a thickened, dry, and scaly condition. As the surface scaled off it was replaced by a bright red, weeping eczematous area, which eventually involved the whole scrotum but did not extend to the thighs. The surface at this time had a remarkable resemblance to the skin of a strawberry and was known as the 'strawberry' dermatitis.

The symptoms were intolerable itching, followed by an equally intolerable burning sensation.

Thiamin had no effect on this condition. Nicotinic acid appeared of mild benefit. Better results were obtained with a B-complex capsule or parenteral B-complex, both of which contained riboflavin. In the Tokyo group, the condition persisted for some time but only in a mild, chronic, dry state and improved to insignificance on the generally better diet in the first half of 1943.

Apart from the primary disability, this scrotal dermatitis was of importance as a site for diphtheritic membranes during the latter epidemic, and many cases of this type were seen, with a high mortality.

(*c*) *'Pellagrinous' Erythema*

The first skin lesions of the type long described as typical of pellagra were seen in June, 1942. These assumed the classical appearance of a symmetrical erythema involving exposed and friction surfaces of the body. They were

most frequent on the dorsum of the forearms and hands, and the posterior aspect of the legs. The condition was fairly common throughout the summer of 1942, reached epidemic proportions in the early autumn, and diminished, almost to disappearance, by the end of the year. It recurred to a lesser extent in Hong Kong in later years, but was not seen again in the Tokyo group in Japan. The exhibition of 100 mgm. of nicotinic acid per os daily, for three days, resulted in a dramatic disappearance of the lesion.

(*d*) *Angular Stomatitis*

Denuding of mucous membrane and fissuring at the corners of the mouth were seen to some degree in the summer of 1942, associated with the stomatitis described above (*a*). Generally, however, this was a later manifestation, at which time the fissuring often reached a severe depth and finally healed with resultant thin scarring. This was an exceedingly chronic condition, which did not respond at all to nicotinic acid or thiamin, but definitely improved on B-complex (thiamin, nicotinic acid, and riboflavin).

(*e*) *Ecthyma*

Beginning in June, 1942, an ulcerating, ecthymatous skin lesion made its appearance and continued to occur throughout 1942, and into the second phase in the Hong Kong group, although it was of minor importance in its severe form in the Tokyo group. Many of the features of this complaint resembled the usual description of the so-called tropical ulcer.

The usual site was the anterior or posterior aspect of the leg, or the lateral aspect of the thigh, and the specific lesion was a deep, cleanly punched-out ulcer with overhanging edges, which laid bare the deep fascia. Penetration beyond the latter depth was not seen. It was extremely resistant to local treatment but would heal after a period of months, leaving a depressed, pigmented scar.

It is probable that this lesion was intimately associated with the general nutritional disturbance, but the exact causative factor was not determined. At one time it was felt that vitamin C contributed to healing, but this opinion was merely of the status of an impression.

(*f*) *Conjunctivitis*

Conjunctivitis with rapid corneal ulceration began in August, 1942, and reached epidemic proportions by November, 1942. At that time it ceased almost overnight, coincident with a substantial increase in animal protein in the diet and the receipt of shark oil, said to be rich in vitamin A. This is more fully described under Visual Disturbances (X).

(*g*) *Glossitis*

The evidences of nutritional disturbance in the tongue began in the early summer of 1942. They consisted of redness and soreness of the margins and tip, with undue prominence of the papillae. This spread to involve the whole dorsum, and the papillae atrophied leaving a smooth, shiny, bright-red surface. By early autumn of 1942, many of these cases had progressed to the 'geographic

tongue', with the formation of deep furrows, mainly running in the direction of the length of the organ. Examples of this type persisted for long periods and throughout internment a substantial proportion of both the Hong Kong and Japanese populations exhibited the remains of furrowing, and abnormalities of the margin and tip, with tenderness. The chronic stage, however, was never so painful as that of the early period.

There was no response to thiamin and while nicotinic acid improved the condition it did so only very slowly.

(*h*) *Paranasal Dermatitis*

This began to occur commonly in the early fall of 1942, and was seen, not infrequently, from that time forward in the Hong Kong group, although it did not occur in the Tokyo group after January, 1943.

The condition was a seborrhoea-like lesion in the folds between nose, lips, and cheeks. Thiamin and nicotinic acid had no effect but treatment for one week with B-complex capsules (containing riboflavin) produced a cure.

(*i*) *Keratosis*

Extreme dryness, thickening, and roughening, and brownish pigmentation over pressure points (as the knees and elbows) occurred in the skin in the summer of 1942. The hair follicles appeared very prominent and horny, and the hairs were not properly extruded. This never gave rise to any serious discomfort but persisted very generally throughout internment. From previous descriptions it would appear to be associated with a deficiency of the fat-soluble vitamin A.

VIII. Breast Tumours

We mention breast tumours in passing because of their possible interest in relation to a connection between nutritional lack and hormonal activity.

Tumours of the male breast began to appear with moderate frequency in the early summer of 1942. They continued to be present through the autumn of 1942, were rare and sporadic during the second phase of internment, and again assumed increased frequency after release and return to European food.

They consisted of firm, discrete, single nodules, unilateral in most cases, averaging 2 to 4 cm. in diameter, flattened from anterior to posterior like a button, situated in the subcutaneous tissue, and not firmly attached to skin or deep fascia.

They were, at first, tender, later generally symptomless, though a few proceeded to abscess formation. At operation a few were observed, and appeared in the gross to resemble fibroadenomata. Most, however, finally resolved without treatment.

Our opinions as to their aetiology are purely theoretical and will not be discussed here.

IX. Gastrointestinal Complaints

Anorexia, nausea, and diarrhoea, were seen to accompany other symptoms of nutritional disturbance at a very early date. Indeed, anorexia was thought

to be one of the first phenomena of nutritional breakdown associated with the oedema and paraesthesia of April, 1942.

The exact relationship of these complaints to avitaminosis is difficult to establish. Anorexia and nausea were not surprising considered in relation to a diet of musty, maggot-infested rice and weedy vegetables, and many other psychic factors undoubtedly exerted a considerable influence. The position of diarrhoea as cause or effect of avitaminosis has been mentioned previously. Moreover, as time went on (and as has been confirmed since release) anorexia, dyspepsia, and flatulence were common concomitants of amoebiasis.

However, certain observations are worthy of record.

Anorexia generally responded very well to the administration of thiamin. In fact, even in those who had a normal appetite, the desire for food was frequently increased during a course of vitamin B_1. Many men objected to being treated with thiamin for other complaints, on the grounds that it created an appetite that they had no means of gratifying.

Many autopsies were done on men who died while suffering from diarrhoea and signs of avitaminosis. No microscopic sections could be made but the gross appearance of the bowel was characteristic. The gut lining was smoothly flat and parchment-like, and to palpation lacked the velvety sensation of normal bowel mucosa. One assumed that the intestinal villi had largely disappeared. This offered a vivid basis for what was well recognized, that is that the availability of foodstuffs and medicines administered per os was markedly decreased from normal, and confirmed the choice of the parenteral route whenever possible, for its markedly superior effect.

Following the return to Canada many of the men continued to complain of anorexia and nausea, although they were receiving large amounts of the B-complex by mouth and parenterally. Fractional gastric analyses were done on many, generally without the stimulation of histamine. Although the tendency was to a low free hydrochloric acid, it was felt that the change was not significant.

X. Visual Disturbances

Deficiencies affecting vision were widespread, and, for descriptive purposes, may be divided conveniently into two classes: the acute and the chronic.

(*a*) *Acute*

These were of the type in which a nutritional deficiency reduced the resistance of the corneal conjunctiva to infection and the latter very frequently induced a rapid ulceration of the cornea.

The condition began in the summer of 1942 and reached its peak in November of that year, after which it very rapidly disappeared. During this period the men were performing pick-and-shovel labour in sandy soil and local irritation of the eye was of common occurrence. However, in passing, it is of importance to note that in the Tokyo group, 1943-45, many of the men worked at oxyacetylene welding without protective glasses, which gave rise

to a severe conjunctivitis, and others at steel welding, which resulted in many foreign bodies in the cornea, yet neither of these severe conditions resulted in the acute syndrome seen in the fall of 1942.

This syndrome began with a complaint of itching or burning of the eyes with photophobia, and on examination a moderate conjunctivitis would be discovered. Often at the first examination, or frequently shortly afterwards, a pin-point ulcer could also be discerned on the cornea and this would progress to a large ulcer, often as big as the iris, in the incredibly short time of four to eight hours. This was accompanied by very severe pain and photophobia, but little constitutional disturbance.

Prior to, and during October, 1942, treatment was confined to rest in a dark room, local wet heat, instillation of boric acid, mercurochrome, or acriflavine, and dilatation of the pupil with atropine.

A number of these cases resulted in gross permanent scarring with subsequent interference with vision. In all, 7.6% of the camp population of about 1500 men suffered from corneal ulceration. Perforation of the ulcer in two cases necessitated enucleation of the eye.

In November, 1942, a supply of shark oil, said to be the equivalent of halibut liver oil in vitamin A content, became available for treatment. This was given routinely to all cases of conjunctivitis in dosage of 5 minims t.i.d., and resulted in a significant decrease in the number of cases that progressed to ulceration. The incidence of conjunctivitis, however, continued unabated.

In December, 1942, the arrival of Red Cross food provided a marked improvement in the animal protein and, to a lesser extent, the animal fat content of the diet. From the same source at this time a supply of caramels, reinforced with vitamin A, were received and issued generally. Coincident with this there was a sudden and complete cessation of the complaint of conjuctivitis and corneal ulceration. Both in Japan (*vide supra*) and in Hong Kong, conjunctivitis was seen in the second phase but this severe syndrome never recurred.

It was felt that the causative factor in the corneal lesion was probably a mixed deficiency of vitamin A and of one of the B-factors, which, judging from other sources, was perhaps riboflavin.

(*b*) *Chronic*

The second and more serious condition affecting vision was a type of chronic failure. The complaint in these cases was a gradual blurring of visual acuity with no pain or photophobia. It was first noted in September, 1942, was very common in the remainder of that year, and reached a peak in the Hong Kong group in the early spring of 1943, although this peak was not so noticeable in the Tokyo group. Cases continued to occur in both groups, however, until the end of internment.

Examination disclosed decreasing visual acuity, concentric contraction of the visual fields, and, frequently, central or paracentral scotomata. Unfortunately, an ophthalmoscope was not available for use in the camp but occasional

reports from an outside hospital on these cases stated that optic atrophy was present. One of us had a chance to study many of these cases at a central prisoner hospital in the Tokyo area in 1944, and in these well-developed examples, typical optic atrophy and pallor of the temporal side of the disc was observed.

In the Hong Kong group monthly examinations of visual acuity were carried out after July, 1943, and following return to Canada complete ophthalmological studies have been done. During the period of internment 60.7% of the camp exhibited decreased visual acuity. After repatriation 16.5% showed pathological changes in the optic disc and 6.1% were found to have a vision of 20/200 or less in one or both eyes. The results of two examinations carried out on the Tokyo group are also included here; (the percentages are cumulative).

	April, 1943 (No. examined, 146)	September, 1944 (No. examined, 463)
Both eyes V : 20/ 40 or less	105—72%	181—39%
One eye V : 20/100 or less	74—51%	60—13%
Both eyes V : 20/100 or less	31—21%	20— 6%
Both eyes V : 20/200 or less	6	2

These cases generally did not improve on the small doses of thiamin available, and even in a few selected severe cases, where thiamin and vitamin A were used, in doses of 20 to 30 mgm. intramuscularly of the former, and 5000 to 10,000 units orally of the latter, daily, for two to three months, improvement was either very slight or entirely imperceptible. Moreover, many cases are on record where the condition developed during a time when thiamin was being given in small doses for oedema or some other symptom. However, it was usual for progression of the complaint to be markedly slowed, or halted, under prolonged small doses of thiamin (1 to 2 mgm. intramuscularly, daily).

It was our opinion that this would be the paramount deficiency defect to fail to recover after repatriation, because severe nervous damage seemed more prominent here than in other parts of the nervous system, and it has, indeed, been the most resistant single complaint.

The specific symptom of 'night blindness' may be mentioned here. It appeared, at first, in the late summer of 1942, being of moderate extent for the rest of that year and continuing chronic, but of mild importance, during the second phase. The B-factors available had no effect on this complaint, but it gradually improved on more varied diets.

XI. Auditory Defects

Damage to the VIII cranial nerve, associated with nutritional deficiencies, was not obvious during the period of internment. Only two cases of nerve deafness, possibly attributable to avitaminosis, were seen, and one of these was in an individual who had suffered widespread paralysis following

diphtheria, which he had contracted while suffering from severe general signs of avitaminosis.

Since the repatriation of the group many audiometric examinations have been carried out. These suggest that there is widespread damage to the VIII cranial nerves, usually involving the higher ranges of frequency, and not diminishing perception of ordinary conversational voice. It is hoped that a further report on this problem may follow.

XII. Cardiac Changes

A very common sign of cardiac involvement was tachycardia, and this was first noted in the late summer of 1942. By November, 1942, it was almost universal. The majority of cases made no complaint and were noted on routine examination.

The earlier cases received a good deal of attention and it is possible that this formed a psychological basis for complaint. However, when the condition assumed widespread proportions, it was no longer possible to grant respite from work to all who exhibited tachycardia. An arbitrary method of selection was laid down. A resting apex rate of 130 or more per minute was considered cause for rest from work parties. If the rate was 100 to 120, without associated symptoms of cardiac distress, no special treatment was provided. Apex rates of 120 to 130 per minute were assessed in the light of other findings. In these cases of tachycardia, auscultation generally revealed a tic-tac rhythm.

In addition to, or separately from, tachycardia, many cases showed other disturbances of cardiac rhythm. Early in the summer of 1942, extrasystoles on effort were of common occurrence, and this continued as a relatively benign sign throughout both phases of internment. From the late summer of 1942 onwards, common cardiac arrhythmias were paroxysmal runs of extrasystoles, paroxysmal tachycardia, and partial heart block, the latter being particularly prone to appear during the course of acute infections such as pneumonia.

Clinical evidence of cardiac enlargement was relatively infrequent. In those exhibiting the chronic picture of heart involvement, increase in size was not a part of the syndrome. Indeed, even in acute episodes, with sudden left-sided failure, enlargement was by no means constant.

Precordial pain was rare and quite benign, of the type not uncommonly seen in advanced rheumatic heart disease in young individuals, viz.: a mild, aching, persistent pain at, or just medial to, the apex. This, being combined with other evidences of disturbance of the heart, was felt to be of cardiac origin.

Changes of the quality of the cardiac sounds included, most commonly, a marked accentuation and echoing of P2. This usually responded early to treatment. Much more uncommon was a similar change in M2. Soft, occasionally rough and harsh, systolic murmurs were found not infrequently at both base and apex of the heart. In the light of the usual lack of clinical enlargement, it was felt that some other cause, such as the theoretical relaxation of valve rings, was responsible for most of these.

Treatment of all these complaints was on the line of reduction of load and addition of thiamin, with whatever general supportive feeding was available. Thiamin was used in dosage of 1 to 50 to 100 mgm., intramuscularly or intravenously, depending on the gravity of the complaint and the amount available. All these abnormalities responded to thiamin. Cardiac collapse, however, was the common immediate cause of death in many infective processes and occurred under much less load than in individuals of the same age group in Canada. It was our impression that the cardiac age under these conditions was advanced some 20 years.

Since return to Canada electrocardiographic examinations have revealed low voltage in about 17% of the repatriates.

XIII. Psychological Aspects

It has been stated that one of the symptoms of the B-complex deficiency is mental depression. Certainly mental depression was of common occurrence during the period of internment. The authors, however, feel that they are unable to establish any direct relationship between B-complex deficiency and this condition.

Continual bombardment with Japanese propaganda, consistently bad reports on the progress of the War over a period of many months, oppressive living conditions, physical punishment, widespread disease, emaciation, and numerous deaths among comrades played an obvious role in the production of mental depression in the men.

During the first phase, 1942, depressive states that were effective in producing abnormal conduct were far more common than in the second phase. A number of these cases adjusted to their changed environment, and a number, adding peculiarities of behaviour to the other factors attacking them, died. Thus the second phase contained relatively few of the psychoneurotic pictures. This was also observed by medical officers from all parts of the Far East, with whom we conversed after release.

Petty theft, both from their fellows and from the Japanese, was endemic. The two main objectives prompting this were food and/or tobacco or both. Punishment by the captors was so severe, and often induced for such trivial causes, that a disregard for all types of retribution was rapidly acquired and must, in many cases, still exist.

Yet, on the whole, despite the tremendous individual drive for self-preservation it was remarkable how the vast majority of the men could be welded into an attitude that regarded a state of general group co-operation as a prime factor of conduct.

No less admirable, and particularly obvious in the second phase, was the high morale of most individuals and the excellent adjustment to a way of life poles removed from our usual conceptions.

We feel that no noteworthy emotional change is connected with vitamin B deficiency, but indeed, under the circumstances, if one drew any conclusion, it would necessarily tend to the euphoric rather than the depressive side.

Seven cases of schizophrenia were recognized during the whole period of internment. The first of these was diagnosed in June, 1942, the last in the spring of 1945. It is felt that avitaminoses played no significant role in their production, although the general camp conditions probably contributed to their breakdown. Manic-depressive psychosis was not seen.

XIV. Example of Morbidity Rates

The relative and absolute importance of various syndromes of the above types in rendering men unable to work may be gauged from the following records.

Fig. 2 is comprised of graphs, during 1943-44, of the morbidity rates of the five principal disease-groups causing disability in the Tokyo camp of 500 men. A comparative graph of the mean weight, which reflected rations, is included. Certain comments are to be made:

(*a*) Disability due to avitaminosis-B gradually improved throughout this period, despite the variable mean weight. However, the diet was always relatively more varied in grain and beans than the diet in the early Hong Kong period. Thus it is again obvious that the variety of the diet is more important than its caloric content.

(*b*) Gastrointestinal disability showed no relation to mean weight. It did, however, exhibit a seasonal incidence, being more marked in the summer months.

(*c*) The severity of skin infections (and injuries, which were relatively constant) gradually decreased throughout this period, and as in (*a*) it appeared that the variety of the diet was of more importance than the caloric content.

(*d*) Arthritic disease was of minor importance and exhibited only a seasonal incidence.

(*e*) Respiratory infections showed a seasonal incidence, being most marked during the winter months. However, these were much more severe in the winter of 1943-44 than in the previous winter, and this appeared to be due to a lowered resistance following the period of increasing malnutrition in the last six months of 1943.

D. The Deficiency Syndrome

Having considered the development of the various signs and symptoms of the deficiency syndrome in, as it were, piecemeal fashion, let us now view the picture as a whole.

To do so we shall describe:

(*a*) A case history taken in the spring of 1943, which can well serve as a model for the average prisoner of war.

(*b*) Table III to show the extent and variety of signs and symptoms at the same period.

(*c*) An acute phase of the syndrome that occurred in a few cases.

(*a*) This is a description of Rifleman H. in the spring of 1943. He is not as well as some of his fellows, but better than others. He can, and does go out on work parties, at least part of the time. He is not ill enough to occupy a hospital bed.

He is very thin, having lost 20% (36 lb.) of his average body weight previous to internment, and he appears about 50 years old although his actual age is 30.

His skin is dry and rough, loose and inelastic, and subcutaneous fat is absent. There is an area of brownish pigmentation over his malar prominences, and the bridge of the nose and the elbows. He has had a 'pellagrinous' dermatitis on the posterior aspect of the knees and the dorsum of the wrist, but this has now cleared up. There are cracks at the corners of the mouth. At the nasolabial folds there are patches of a seborrhoea-like dermatitis. He has a deep ulcer on the calf of the left leg. His tongue is sore, smooth, and very red at the margins and tip. (Later the dorsum of the tongue became deeply fissured.) The buccal and pharyngeal mucous membranes are congested. Two teeth are chipped from biting on pebbles in his rice, and several other teeth are grossly carious so that it is difficult for him to chew his food properly.

The pupils are equal in size and react to light and accommodation. He complains that he cannot read ordinary print but he can make out the newspaper headlines. His vision is R. 20/80, L. 20/100. Bright sunlight causes excessive lachrymation, and he wears dark glasses when he can get them.

He complains of a sensation of constriction, like a band, around his chest. His apex rate is 118 per minute. There is no cardiac enlargement. Auscultation reveals tic-tac rhythm.

He has a mild, dry, unproductive cough but his chest is clear to clinical examination.

Examination of his scaphoid abdomen reveals only mild tenderness over the caecum and sigmoid colon, with borborygmi on pressure. Although his history includes malaria with two relapses, the spleen is not palpable. He has just recovered from an attack of diarrhoea. (His subsequent history showed that he had repeated attacks of diarrhoea.)

He states that both lower extremities are numb from mid-thigh level to the toes. Sensation to light and deep touch, and pin-prick is decreased in this area. The toenails are brittle and markedly thickened. The right toe is deformed, where a trophic ulcer has healed. The patellar reflexes are absent, position sense and vibration sense in the feet are diminished. He exhibits Rombergism. He states that he staggers when trying to walk in the dark but manages moderately well in the daylight. Two months earlier his feet were very painful but this has been greatly relieved since the numbness has supervened. He also has some numbness of his hands, particularly of the fingertips. This makes him clumsy, so that he has trouble trying to roll a cigarette.

Only by direct questioning is nocturnal frequency elicited. This has disturbed his sleep for so long that he regards it as an integral part of existence. He smiles quite readily and does not appear to be greatly concerned about the usual anxieties of life.

This man has received thiamin hydrochloride, 5 mgm. every second day, since mid-October, 1942. In November and December he received a total of 1.0 gm. of nicotinic acid in dosage of 20 mgm. daily or every two days.

(*b*) Table III presents a composite picture of major signs and symptoms of nutritional deficiency from a group of the 500 men in the Tokyo camp in the first half of 1943. At this period they were enjoying the peak diet of the

TABLE III

TO SHOW PERCENTAGE INCIDENCE, VARIETY, AND DISTRIBUTION OF SIGNS IN THE DEFICIENCY SYNDROME IN 60 MEN EXAMINED

Sign or symptom	Dates of examinations											
	February, 1943				April, 1943				June, 1943			
	Total	Severe	Moderate	Mild	Total	Severe	Moderate	Mild	Total	Severe	Moderate	Mild
Nausea	18	18			5	1.7		3.3				
Anorexia	43	43			12	5.3		6.7	6.7			6.7
Chronic diarrhoea	17	17			3.3	3.3			10			10
Pain in lower extremities	100	100			98	5	80	13	37		17	20
Patellar reflex increased	17				15				1.7			
Patellar reflex decreased	60				6.7				6.7			
Ataxia	50	50			18	15		3	3.4	1.7		1.7
Oedema	17	12		5	5			5	32	6.7		25
Calf tenderness	77	77			40	33		6.7	5			5
Signs of cardiac involvement other than tachycardia	60				15				10			
Tachycardia												
(Over 100/M)	53				5.5							
Over 120/M	11											
110–119/M	15				1.1							
100–109/M	27				4.4							
90– 99/M	20				17.6							
70– 89/M	24				76.9							
60– 69/M	3											
Numbness												
Lower extremities	80	80			66	63		3	20	5		15
Upper extremities	77	77			27	27			8	1.5		6.5
Trunk	52	52			8.3	8.3			1.7	1.7		
Face	30	30			1.7	1.7			1.7	1.7		

whole internment, having just arrived in Japan from Hong Kong. This diet provided about 2800 calories daily, made up of carbohydrate 583 gm., fat 16 gm., protein 86 gm., of which 3.9 gm. of the latter were from animal sources.

The first examination recorded here was in early February, 1943, and included 60 men. During the following two months, till April, 1943, 33 of the worst of these men received 3 mgm. of a Japanese brand of thiamin, intramuscularly, daily, and the remainder received 3 mgm. every fifth day.

The second recorded examination was carried out on the same 60 men in early April, 1943, that is, two months later.

In June, 1943, that is after a further period of two months, the 60 men were again re-examined. Of these, 45 had continued to receive thiamin in dosage of 3 mgm. intramuscularly, daily, and 15 had received 3 mgm. every fifth day by the same route.

These observations, as shown in Table III, indicate in percentage figures the incidence, distribution, and variety of major signs and symptoms of the deficiency syndrome. Certain comments may be made in explanation of this table:

1. The gastrointestinal symptoms of anorexia, nausea, and diarrhoea show a marked improvement in the four-month period.

2. Signs of cardiac involvement are shown in two ways, viz.; as tachycardia, and as other signs. The latter were largely accentuation of P2, but not infrequently included accentuation of M2, tic-tac rhythm, paroxysmal tachycardia, isolated or paroxysmal runs of extrasystoles, and partial heart block. Systolic murmurs, loud and rumbling in character, were occasionally heard at both mitral and aortic areas.

Such signs were noted, in February, in 60% of cases. In April this figure had been reduced to 14%, in June to 10%, and these were almost exclusively other than accentuation of P2, which had almost entirely disappeared. It may be concluded that the latter is one of the first signs to disappear with the onset of recovery.

Tachycardia has been arbitrarily set as resting apex rate of 100 per minute. The incidence of such tachycardia is shown, as well as a breakdown of apex rates covering a wider range. The figure for tachycardia in the June examination is not available.

3. Pain, of the 'electric-shock' type, was at this time almost exclusively confined to the lower extremities. The grading as to severity was made on the basis of the man's statement and observations of his behaviour, and obviously shows a marked improvement.

4. Subjective numbness and hypoaesthesia were distributed in 'glove-and-stocking' areas of the extremities, in band areas of the trunk, and in the 'muzzle' area of the face. The percentage distribution of these various areas is shown. It will be noted that the gradient runs from superior to inferior, which was also the track followed in recovery.

5. Respecting the patellar reflex, it has already been pointed out that involvement proceeded through hyperactivity, to hypoactivity, to loss, and that recovery retraced this path. In Table III the term 'decreased' includes both hypoactivity and complete absence.

6. Ataxia was manifested by Rombergism, and, in severe cases, by a wide-based, high-stepping, toe-slapping gait.

7. Oedema was most commonly seen in the lower extremities, next in the skin of the face, and next in the abdominal cavity. From the figures in Table III it is evident that oedema varied considerably from time to time. It paralleled, far more rapidly than any other sign, gross decreases in diet or increases in activity. It was always more marked in hot weather, and the increase in the month of June was an expected one.

8. Abnormal calf tenderness was one of the commonest and most constant signs associated with avitaminosis = B.

From the data presented it can be seen that in a short period of time (four months) there was a marked improvement in the major signs and symptoms of the deficiency syndrome. This occurred on a type of diet and a therapeutic regime that was grossly inadequate, judged by Western standards. Such experience, repeated many times over a period of almost four years, led us to make a favourable prognosis of the syndrome under adequate therapy, even when it was of long standing. There was the outstanding exception of visual failure due to optic atrophy about which we were very pessimistic. The results on adequate treatment since return to Canada have justified, generally, both predictions.

(*c*) *Acute Multiple Peripheral Neuropathy*

From Table III it must not be concluded that the progress of recovery in the deficiency syndrome was invariably smooth and uninterrupted. Decreases in diet, which were frequent, always resulted in an exacerbation of the chronic complaints. In addition, the following is a brief description of a condition that was felt to be an acute syndrome due to B-complex deficiency. It was seen, in Japan, in the first half of 1943 and affected six cases. It has been labelled, tentatively, Acute Multiple Peripheral Neuropathy.

All six cases gave a history of mild deficiency symptoms over a period of months before this acute episode. These symptoms were those of a moderate type of 'electric feet', but none had had as severe symptoms as many of their fellows. At the time of onset of the acute picture five were relatively well nourished, one relatively very malnourished. The five former had continued to work up to the time of the episode to be described, the latter one had been off work because of general debility.

The first complaint was of subjective stiffness for 12 to 48 hr. This was followed by great muscle weakness, rapidly progressing for a period of one to two hours. Where the stiffness had been noted for a sufficient period, it had been most marked after resting, as in the morning on rising, and had improved after exercise. Subsequently, the acute paresis was present in five cases on awakening from sleep, and in the sixth case it came on while the man affected was walking home from work at night. In all six cases the paresis originated in the lower extremities, and in four cases it extended, during the period of rapid progression, to involve the lumbar muscles and the upper extremities as well.

Examination at this time showed impaired position sense in the lower extremities. There was also marked paresis or complete paralysis, hypotonia, depression of the deep reflexes, and patchy hypoaesthesia to light touch and pain stimuli in the areas involved. In the four cases that showed extension to the trunk, the abdominal reflexes were also decreased. The signs were more extreme distally than proximally, and were not necessarily symmetrical, quantitatively or qualitatively. One case showed hyperactivity of the deep reflexes for a few hours at the onset before the progression resulted in impairment. The superficial reflexes were undisturbed and the Babinski response was not present.

Bradycardia existed in one case and disappeared during the course of treatment. Two patients had, at the onset, extrasystoles, which also later cleared up.

The course of the disease was afebrile in all.

Treatment consisted of bed rest, light massage, the addition of tinned Red Cross meat to the regular diet, and thiamin intramuscularly in such quantities as were available. The usual dosage of thiamin was 20 mgm. daily, for the first few days, followed by 3 mgm. daily. At some periods no thiamin was available.

Under such treatment the ascending wave of involvement receded rapidly. After two or three days the only parts affected were the lower extremities, and occasionally the distal portion of the upper extremities. After partial recovery of the myasthenia the deep reflexes generally returned to normal within a week, and the patchy hypoaesthesia also usually disappeared after this time.

A more gradual progressive improvement followed this initial phase with, in five cases, complete objective recovery within an interval of four to eight weeks. It was soon found by experience that, if such exercise as walking for any extended distance was indulged too soon upon apparent recovery, the stiffness and other symptoms recurred. Consequently these cases were kept at very light activity for a month or more after they were allowed up, with no obvious complaints.

The sixth case, who was severely malnourished at the onset of the acute episode, was treated similarly to the above. There was a very gradual improvement over a period of six weeks, at which time the supply of thiamin became exhausted. He then went slowly downhill and died, after nine weeks, with a very severe bulbar and peripheral asthenia.

In Hong Kong 12 similar cases were seen in the spring of 1944. These, however, were transferred to a hospital outside of camp and were not followed to completion by either of the authors, for which reason they are not reported here.

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They also thank the Statistical Section of the Army Medical Directorate for a painstaking analysis of case history sheets.

STUDIES OF SHOCK PRODUCED BY MUSCLE TRAUMA

III. THE EFFECT OF SERUM, ISINGLASS, GLUCOSE, CERTAIN SALTS, AND ADRENAL CORTICAL HORMONES ON SURVIVAL[1]

By R. A. Cleghorn[2]

With the Technical Assistance of Walter Cowan

Abstract

The effect of the administration of dog serum, isinglass, and of glucose, certain salts, adrenal cortical hormones, and of water on dogs subject to severe muscle trauma has been investigated. Isinglass was found to be as efficient an agent as dog serum in restoring the blood pressure and in prolonging life. The effectiveness of transfusion was not increased by giving amounts in excess of 45% of the calculated blood volume nor by prolonging the transfusion from one-half to three and a half hours. Intravenous injection of hypertonic saline before transfusion with a blood substitute raised the blood pressure but did not lengthen survival, and pulmonary oedema was more frequently observed in dogs so treated. The addition of glucose to the blood substitute produced neither permanent benefit nor ill effect. Some of the animals died despite high blood sugar levels resulting from the infusion of glucose. The addition of sodium bicarbonate and calcium gluconate to the transfusion fluid, singly or in combination, did not affect the blood pressure or survival. The ingestion of large quantities of water by mouth after transfusion increased the average duration of life and improved the chance of indefinite survival. The most important single criterion as to whether a traumatized dog would survive indefinitely following transfusion was the level of blood pressure at the time transfusion was given. Indefinite survival of dogs transfused after the blood pressure had fallen below 70% of the initial pressure was exceptional. Those treated before the pressure had fallen so low had an even chance of survival. The administration of adrenal cortical hormones in relatively large amounts had no apparent effect in prolonging life in dogs transfused after the blood pressure had fallen to less than 60% of the initial level. Of eight dogs transfused when the blood pressure was between 60 and 70% of the initial pressure and then treated with carbohydrate-active preparations of the adrenal cortex, four survived indefinitely. None of the control animals with the same blood pressure range survived when treated by transfusion alone. The finding that dogs subject to muscle trauma are clinically sicker and less likely to survive at blood pressure levels successfully endured by bled dogs is discussed. The importance of the impaired blood flow in splanchnic viscera is considered in relation to metabolic changes. Changes in the urine of these dogs are described, and it is concluded that suppression of renal excretory function did not contribute significantly to death following trauma. Impairment of the renal pressor mechanism is considered to be a possible cause of the cardiovascular failure, probably in conjunction with impaired function of the adrenal cortex and toxic substances released from damaged tissues.

In the first paper of this series (8) it was pointed out that some dogs died between 24 and 80 hr. after trauma. Hence the criterion of successful therapy had to be extension of life well beyond any period at which death could be attributed to remote effects of trauma. In the present paper, the results of transfusion and various ancillary forms of treatment will be described. Dogs that were vigorous and eating well at the end of four days were considered as surviving indefinitely.

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Methods

Most of the methods employed have been described earlier (8). Serum was obtained by bleeding large dogs aseptically into large paraffined centrifuge tubes. The isinglass (21) was made up from the powder as a 4% solution in normal saline, and then autoclaved. The calcium administered was a 10% solution of gluconate of calcium (Calcium-Sandoz). The adrenal cortical extract preparations used (Wilson, Upjohn, and Connaught Laboratory) were assayed on dogs and showed excellent and comparable potencies.

Since the initial (carotid) blood pressure varied considerably in different dogs, the pressure at the time treatment was started is expressed as a percentage of the initial pressure.

Results

There was no apparent difference between the effectiveness of serum and isinglass in dogs with hypotension following muscle trauma. Both caused a sustained rise in blood pressure but there were relatively few dogs so well restored that they made a complete recovery.

Dogs becoming hypotensive within five hours of trauma responded to transfusion in the following way. If the blood pressure had reached a level of about 45% of the initial pressure (commonly 55 to 75 mm. Hg), there rarely was a return of the blood pressure to initial level or restoration of conscious activity. A persistently rapid heart rate was a constant accompaniment and was not affected by transfusion. These animals also commonly showed copious loose stools. Death occurred without concentration of the blood after transfusion. At autopsy, oedema of the lungs was apparent in some animals. The intestinal mucosa was generally severely congested and the adrenal cortex haemorrhagic.

The dogs that did not show so severe or so early a drop in blood pressure frequently had a return of conscious activity before their pressure finally declined. If transfused while the pressure was above 45% of the initial, an excellent response was obtained, a sustained rise in pressure and considerable prolongation of survival resulting. Loose stools were uncommon in such cases. The rapid heart rate fell following transfusion though it did not return to normal levels. The packed cell volume usually rose only a little and the blood pressure declined several hours before death. In such cases the lung and intestinal mucosa changes were slight at death but the adrenal cortex was nearly always swollen and showed severe confluent haemorrhage throughout.

Dogs transfused before the pressure had fallen to less than 60% of the initial level showed an even more uniform response: rise in blood pressure to normal levels; a concurrent increase in consciousness and co-ordinated activity; and prolonged survival. Indefinite survival seemed to depend upon the transfusion being given before the pressure had fallen below 70% of the initial pressure.

The number of dogs receiving serum was practically the same as the number receiving isinglass in the different groups of experiments. Since the duration of survival seemed to be quite independent of the blood substitute used, no special reference will be made further to one or the other in the text.

I. The Effect of Serum or Isinglass, Whole Blood, Glucose, and Certain Salts on the Survival of Traumatized Dogs

Group A: Serum or Isinglass

Twenty-two dogs were treated with serum or isinglass only, no water being given in the first 24 hr. following trauma. In the majority of cases transfusion was started when it appeared from the blood pressure and heart rate changes previously described (8) that death was certain within one-half to one hour. The blood substitute was given quickly at first, then slowly. In most experiments the total amount was run in in one and a half hours. In some, as long as three and a half hours was taken, the final portion being given as a slow drip. There was no relationship between the duration of survival and the duration of the transfusion. The usual amount of blood substitute given was 45% of the calculated blood volume, though one dog received 84%, two received 59, and two 51%. Those receiving the larger amounts did not survive any longer than the others. The essential data are given in Table I, Group *A*.

Group B: Whole Blood

Four dogs received citrated, fresh, whole, dogs' blood, transfused in the same manner as Group *A*. One of these four dogs received transfusion of two parts whole blood and the remaining three parts serum. The duration of survival was no greater than in the previous series treated with serum or isinglass. The data are summarized in Table I, Group *B*.

Group C: Adrenal Cortical Hormones and Serum or Isinglass

Thirteen dogs were treated with adrenal cortical hormones as well as with serum or isinglass. The literature on the use of adrenal cortical hormones in shock has been reviewed by Swingle *et al.* (19, 20). Five of our dogs received aqueous cortical extract injected intravenously in divided doses, or added to the intravenous sólution. Four were given desoxycorticosterone acetate (D.C.A.) intravenously in propylene glycol in divided doses totalling 3 to 7 mgm. per kgm. In this form D.C.A. is very effective in restoring dogs in adrenal insufficiency (7). Four dogs received both cortical extract and D.C.A. in amounts totalling 5 to 6 cc. per kgm. and 3 to 4 mgm. per kgm., respectively.

Survival was not prolonged by this adjuvant to transfusion. Furthermore, two of the dogs treated with aqueous extract as well as three of those receiving D.C.A. had hypoglycaemic blood levels before death. The data are summarized in Table I, Group *C*.

TABLE I

THE EFFECT OF SERUM, ISINGLASS, AND CERTAIN SALTS ON THE SURVIVAL OF DOGS SHOCKED BY MUSCLE TRAUMA

GROUP A — Serum or isinglass

Treatment started: Hours after trauma	Treatment started: Blood pressure, % initial	Life prolonged, hr.
S 5.0	23	8.0
S 2.5	27	15.0
S 1.3	33	2.5
I 4.4	36	7.5
I 2.5	36	0.2
S 2.0	38	2.5
I 4.3	42	7.5
I 2.7	42	10.0
S 3.5	45	15.0
S 13.3	45	4.5
S 1.7	47	5.0
I 8.0	47	14.5
I 2.0	47	2.0
I 1.7	50	2.0
I 3.5	50	6.0
S 4.2	51	45.0
S 5.6	53	25.0
S 2.2	55	Indef.
I 2.0	56	4.0
S 7.6	57	13.5
I 5.0	57	9.0
I 10.8	72	Indef.

GROUP B — Whole blood

B 1.3	25	2.5
B 2.1	40	2.5
B 3.7	48	2.0
B 5.5	53	7.7

GROUP C — Adrenal cortical hormones and serum or isinglass

Treatment started: Hours after trauma	Treatment started: Blood pressure, % initial	Life prolonged, hr.
I 3.3	29	10.0 o
I 6.0	30	40.0 x
S 3.0	30	0.5 o
S 2.5	40	1.5 o
I 4.0	41	5.7 x
S 7.2	43	3.5 o
S 1.1	43	4.0 o
S 3.1	49	11.0 x
I 3.9	51	5.0 *
I 4.7	56	11.0 *
S 4.6	60	4.5 x
S 6.1	60	9.0 *
I 5.0	63	28.0 *

GROUP D — Glucose and isinglass or serum

I 4.0	33	2.0
I 10.0	36	1.5
S 13.7	47	3.7
S 12.5	49	5.0
S 12.6	55	3.0
S 10.7	55	20.0

GROUP E — Hypertonic saline and serum or isinglass

Treatment started: Hours after trauma	Treatment started: Blood pressure, % initial	Life prolonged, hr.
I 1.18	34	5.5
I 3.1	37	3.0
S 11.7	37	13.0
I 2.7	39	3.7
S 3.8	43	1.5
I 6.1	47	4.0
S 3.5	48	11.5
S 4.7	50	4.2
S 3.5	50	11.0
I 4.4	60	30.0
I 6.1	70	5.5

GROUP F — Serum, saline, and sodium bicarbonate

4.5	35	10.0
11.0	45	27.0
7.7	64	9.0

GROUP G — Water per os and serum or isinglass

Treatment started: Hours after trauma	Treatment started: Blood pressure, % initial	Life prolonged, hr.
S 6.8	41	6.5
I 10.2	56	19.0
I 1.8	58	8.0
S 2.7	58	29.0
S 16.5	58	4.0
S 5.2	59	21.0
S 9.7	65	100.0
S 5.3	69	24.0
I 6.6	69	36.0
I 2.2	72	Indef.
I 5.4	75	"
S 6.5	80	"
I 3.5	82	22.0

GROUP H — Sodium bicarbonate, water, and serum

S 3.9	47	2.0
S 4.1	62	27.0
S 3.5	72	Indef.
S 7.3	74	24.0

GROUP I — Sodium bicarbonate, calcium gluconate, water, and serum or isinglass

Treatment started: Hours after trauma	Treatment started: Blood pressure, % initial	Life prolonged, hr.
I 3.0	24	2.5
I 2.7	30	5.0
S 1.8	34	9.0
I 4.0	44	3.0
S 3.0	40	8.0
I 10.8	52	5.0
S 3.0	56	12.0
S 6.0	57	19.0
I 13.6	61	25.0
I 8.6	62	25.0
I 4.1	63	8.0
I 3.0	64	22.0
I 7.3	70	Indef.
S 5.9	76	11.0

*Abbreviations: S—serum; I—isinglass; B—whole blood; o—aqueous cortical extract; x—desoxycorticosterone acetate; *—cortical extract and desoxycorticosterone acetate.*

Group D: Glucose and Serum or Isinglass

In view of the hypoglycaemia frequently observed following transfusion (8), six dogs were given 12 gm. of glucose intravenously just as the transfusion of blood substitute was completed. The basic data on these experiments are given in Table I, Group *D*. No increase in the duration of survival of these dogs resulted. The injected glucose led to a great rise in the blood sugar level. The two dogs that lived the shortest time after transfusion still had blood sugar levels of over 300 mgm. % at death. Three others died with blood sugar levels of below 47 mgm. %. The remaining dog, in which life was prolonged for 20 hr., had a low normal blood sugar value eight hours before death.

Group E: Hypertonic Saline and Serum or Isinglass

Eleven dogs received an infusion of a 3% sodium chloride solution prior to the administration of the usual volume of serum or isinglass given at the usual rate. Scudder (16) is of the opinion that saline relaxes constricted arterioles and consequently is of benefit in shock. An amount of saline equal to 17.4 cc. per kgm. was given in 20 to 30 min.; this resulted in a fairly marked rise in blood pressure. The blood substitute was then given. This combined treatment did not lead to any improvement in the duration of survival, and a number of animals showed signs of pulmonary oedema following the infusion. The data are summarized in Table I, Group *E*.

Group F: Sodium Bicarbonate, Hypertonic Saline, and Serum

Since sodium bicarbonate has been said to relieve the acidosis present in shock and to effect a material improvement (3, 9), it was used in some of our experiments. Three dogs received 0.3 gm. per kgm. sodium bicarbonate added to the same amount of saline as used in the Group *E* experiments. This was followed by administration of serum. There was no demonstrable effect of the alkali on survival as Table I, Group *F*, shows.

Group G: Water per os and Serum or Isinglass

In this and subsequent groups the period of transfusion was reduced to 45 min.

Thirteen dogs were given water following the infusion of serum or isinglass. Treatment was begun when the blood pressure was higher than in previous groups, death being anticipated in one-half to two hours. The dogs that were conscious following the transfusion lapped water offered them. Their intake varied from 25 to 70 cc. per kgm. in the first few hours. Four dogs that were not conscious received water by stomach tube, about 50 cc. per kgm. being given in the first three or four hours. This series showed a definitely longer survival, and more indefinite survivors, than any of the previous groups. This was not due solely to the fact that treatment was begun at a higher blood pressure level since the average duration of survival of all the dogs in the previous groups that had a blood pressure of over 55% of the initial pressure was 12 hr. as opposed to 20 hr. for the corresponding group

in the present series. Three indefinite survivors and a dog that lived 100 hr. were excluded from this calculation. The data on these experiments are summarized in Table I, Group *G*.

Group H: Sodium Bicarbonate, Water, and Serum

Four dogs were given 0.3 gm. sodium bicarbonate per kgm. added to the serum. Water was allowed *ad libitum* after the transfusion. There were no significant results in the behaviour or survival time in this group. The data are shown in Table I, Group *H*.

Group I: Sodium Bicarbonate, Calcium Gluconate, Water, and Serum or Isinglass

Fourteen dogs received sodium bicarbonate dissolved in the blood substitute, as in Groups *F* and *H*. During transfusion a 10% solution of calcium gluconate was injected slowly intravenously, about 0.2 cc. per kgm. being given, on the hypothesis that the calcium ion might offset the deleterious influence of potassium, which is known to be released from traumatized muscle (4, 15). Water was offered when the transfusion was finished and given by stomach tube when not taken freely. There was no improvement in the duration of survival of the dogs in this group compared to others receiving water. The data on this series are summarized in Table I, Group *I*.

II. The Effect of Adrenal Cortical Hormones on the Survival of Traumatized Dogs Transfused with Serum or Isinglass and Given Water

Twenty-one dogs were treated with adrenal cortical hormones as well as with a blood substitute and liberal amounts of water. The results are summarized in Table II along with control data derived from Table I, Groups *G*, *H*, and *I*. Only dogs having a blood pressure at the time of transfusion of 48% of the initial pressure, and above, were selected as controls, since this is the range of pressure of the hormone treated dogs.

1. *Desoxycorticosterone Acetate*

Three dogs received relatively large amounts of desoxycorticosterone acetate: 3.5 to 5 mgm. per kgm. This was given in divided doses: part, dissolved in propylene glycol, was injected intravenously; and the remainder, dissolved in sesame oil, was administered subcutaneously. These dogs (Nos. 27, 30, and 33) had blood pressures of 54, 58, and 60% of the initial pressures, respectively, when treated at 8, 13, and 13½ hr. Post-mortem examination showed massive haemorrhage, swelling, and congestion of the adrenals in all three animals. Life was not prolonged beyond that of comparable controls.

2. *Carbohydrate-active Preparations*

(*a*). Kendall's Substance E (17-hydroxy-11-dehydrocorticosterone) was given to four dogs (Nos. 25, 28, 36, and 42). (See Table II.) This was administered intravenously in a weak alcoholic solution (20) in six to nine doses over the first 12 to 15 hr. following the beginning of the blood substitute transfusion. Since supplies of Substance E were inadequate for further

TABLE II

EFFECT OF ADRENAL CORTICAL HORMONES ON THE SURVIVAL OF SHOCKED DOGS TRANSFUSED WITH SERUM OR ISINGLASS

Control animals*						Animals treated with adrenal cortical hormones								
Blood substitute, etc.	Treatment started				Life prolonged, hr.	Blood substitute, etc.	Treatment started				Life prolonged, hr.	Adrenal preparation (mgm. or cc. per kgm. per day)		
	Hours after trauma	Heart rate	Blood pressure				Hours after trauma	Heart rate	Blood pressure			1st	2nd	3rd
			mm. Hg	% initial					mm. Hg	% initial				
S	3.0	150	76	48	8	S	4.3	128	68	48	13	E 1.3 mgm.		
I Na Ca	10.3	192	84	52	5	I	2.0	200	73	51	11	ACE 7 cc.		
I	10.2	192	87	56	19	I	13.0	113	82	54	20	DCA 5 mgm.		
S Na Ca	3.0	154	89	56	12	I	4.2	162	83	56	15	E 1.5 mgm.	ACE 1 cc.	
S Na Ca	6.0	168	80	57	19	S	6.0	228	98	57	12	ACE 3.7 cc.		
I	1.8	190	82	58	8	I	8.0	160	78	58	6	DCA 5 mgm.		
S	2.7	216	78	58	29	S	7.8	180	84	58	25	ACE 4 cc.		
S	16.5	140	84	58	4	S	6.3	168	94	59	13	ACE 5 cc.		
S	5.2	148	98	59	21	I	13.5	196	86	60	11	DCA 3.5 mgm.		
I Na Ca	13.6	174	92	61	25	I	11.6	160	90	60	Indef.	ACE 6 cc.	4.5 cc.	3 cc.
S Na	4.1	174	84	62	27	S	5.0	162	84	60	"	ACE 5.5 cc.	4 cc.	2.6 cc.
I Na Ca	8.6	224	90	62	25	I	5.1	240	98	61	37	E 3 mgm.	ACE 7 cc.	ACE 4 cc.
I Na Ca	4.1	246	88	63	8	S	3.5	210	95	63	17	ACE 4 cc.		
I Na Ca	3.0	204	110	64	22	I	6.5	116	95	63	Indef.	ACE 5 cc.	2.8 cc.	1.6 cc.
S	9.7	180	100	65	100	I	2.9	204	99	65	3.5	ACE 3 cc.		
S	5.3	174	86	69	24	S	12.5	184	80	66	Indef.	ACE 6 cc.	3 cc.	1.3 cc.
I	6.6	144	93	69	36	I	5.6	256	101	68	11	ACE 2.6 cc.		
I Na Ca	7.3	180	95	70	Indef.	S	8.5	200	91	70	Indef.	E 1.3 cc.	ACE 3 cc.	ACE 4 cc.
S Na	3.5	198	90	72	"	S	5.6	234	90	72	"	ACE 2.6 cc.	2.4 cc.	2 cc.
I	2.2	224	105	72	"	S	3.0	210	98	78	"	ACE 5.5 cc.	2.4 cc.	1 cc.
S Na	7.3	120	82	74	24	S	6.1	192	110	88	"	ACE 3.2 cc.	3.2 cc.	4 cc.
I	5.4	192	102	75	Indef.									
S	6.5	170	104	80	"									
I	3.5	186	100	82	22									

* *Data from Table I, Groups G, H, and I.*

Abbreviations: S—serum; I—isinglass; Na—sodium bicarbonate; Ca—calcium gluconate; ACE—aqueous cortical extract; DCA—desoxycorticosterone acetate; E—17-hydroxy-11-dehydrocorticosterone.

treatment, this was followed by administration of aqueous cortical extract to the three animals that lived longest. There was no evidence that the hormone treatment resulted in significant benefit since only one dog, the one that had the highest blood pressure when transfused, lived indefinitely. The adrenal cortical changes were moderate in two and severe in one of those that died.

(*b*). Aqueous cortical extracts alone were given to the remaining 14 dogs. The extract was added to the transfusion fluid and given subsequently both intravenously and subcutaneously. Six dogs survived indefinitely but in the eight others there was no significant difference in survival compared with the control animals. Adrenal changes in the dogs that died varied from moderate to severe.

The control group and the dogs treated with carbohydrate-active hormone are compared in Table III. Only dogs with blood pressure of 60%, or over, of the initial pressure have been included as there was no evidence of prolongation of life by the hormone treatment in dogs having lower pressure at the time of treatment. Of the 15 controls, five (33%) survived indefinitely.

TABLE III

THE INFLUENCE OF ADRENAL CORTICAL HORMONE ON SURVIVAL OF DOGS DEVELOPING SHOCK FOLLOWING MUSCLE TRAUMA*

Control animals			Animals treated with adrenal cortical hormone		
Blood pressure as treatment started		Life prolonged, hr.	Blood pressure as treatment started		Life prolonged, hr.
mm. Hg	% Initial		mm. Hg	% Initial	
92	61	25	90	60	Indef.
84	62	27	84	60	Indef.
90	62	25	98	61	37
88	63	8	95	63	17
110	64	22	95	63	Indef.
100	65	100	99	65	3.5
86	69	24	80	66	Indef.
93	69	36	101	68	11
95	70	Indef.	91	70	Indef.
90	72	Indef.	90	72	Indef.
105	72	Indef.	98	78	Indef.
82	74	24	110	88	Indef.
102	75	Indef.			
104	80	Indef.			
100	82	22			
Indefinite survivors 33%			Indefinite survivors 66%		

* *Data from Table II. Both controls and hormone treated dogs were transfused with serum or isinglass to restore the blood volume.*

None of the control animals with blood pressure less than 70% of the initial pressure survived. Of the 12 hormone treated dogs there were eight (66%) that survived indefinitely. These results are not striking but closer inspection of the data on these animals shows that four of the eight hormone treated

survivors had pressures less than 70% of the initial pressure at the time of treatment. In terms of absolute pressure, only two of the five controls that survived had pressures of less than 102 mm. Hg at the time treatment was instituted. On the other hand, seven of the eight survivors in the hormone treated group had pressures less than 102 mm. Hg when transfused: two of the dogs had pressures as low as 80 and 84 mm. Hg respectively. There was no significant prolongation of life in the hormone treated dogs having blood pressure levels of less than 60% at the time transfusion was started.

III. Urinary Changes in Dogs Shocked by Muscle Trauma

Untreated dogs that died within 18 hr. of being traumatized rarely passed any urine. At autopsy small amounts could be aspirated from the bladder; these were dark in colour, acid, of high specific gravity, and contained granular, haemoglobin, and hyaline casts.

Transfused dogs showed similarly abnormal urine. Animals that lived but a few hours following treatment secreted little. Those living more than 12 but less than 48 hr. after transfusion passed moderate amounts of urine. This, generally, was as much as that excreted by the transfused dogs that survived indefinitely. Table IV summarizes observations on the quantity of urine excreted by 11 dogs that died and by eight that survived indefinitely. Some

TABLE IV

Urinary excretion in dogs transfused following muscle trauma

Deaths		Survivors
Time from end of transfusion to death, hr.	Urine excretion, cc./kgm./hr.	Urine excretion during first 24 hr., cc./kgm./hr.
29	1.2	1.6
21	2.4	2.1
25	1.3	1.4
20	2.0	1.2
15	1.0	1.6
14	2.0	1.1
26	2.0	4.0
15	1.1	2.0
37	27.0	
18	0.6	
12	0.6	

details of the urinary changes observed in transfused dogs are contained in Table V. The higher specific gravity of the urine of some of the surviving animals is not significant as values as low or lower than in dogs that died were observed among survivors. Non-protein nitrogen estimations were obtained infrequently. The values ranged from 43 to 80 mgm. % in dogs dying up to 36 hr. after being transfused. Only in two instances were levels above 100 mgm. % observed.

TABLE V

COMPARISON OF URINARY CHANGES IN TWO DOGS SUBJECT TO MUSCLE TRAUMA TREATED BY TRANSFUSION

Dog that died								Dog that survived							
Time after transfusion, hr.	Water intake, cc./kgm.	Amount excreted, cc./kgm.	Colour	Reaction	S.G.	Albumin	Blood and casts	Time after transfusion, days	Water intake, cc./kgm.	Amount excreted, cc./kgm.	Colour	Reaction	S.G.	Albumin	Blood and casts
3	53	15	Light Brown	Alkaline	1035	Trace	None	1	100	53	Red Brown	Acid	1020	++	+
17	44	16	Red Brown	Acid	1023	+++	+	2	57	45	Black Brown	Acid	1027	+++	+
25	19	20	Dark Red Brown	Acid	1025	++++	+	3	50	39	Light Brown	Acid	1024	Trace	+
30	27	7	Dark Red Brown	Acid	1033	++++	+	4	45	36	Light Brown	Acid	1035	—	—
37	—	7	Light Red Brown	Acid	1030	++++	+	5	35	46	Yellow	Alkaline	1043	—	—

IV. The Possible Influence of Infection in the Death of Dogs Following Muscle Trauma

It was not practicable to maintain an aseptic technique while taking repeated blood pressure readings from the cannulated carotid artery. This was not held to be a serious matter for it is well known among laboratory workers that dogs are extraordinarily resistant to infection by the intravenous injection of unsterilized solutions. The same is probably true of intra-arterial contamination, which was most likely in this case as the citrate in the connection to the mercury manometer was not sterilized. However, care was taken to have the blood substitutes sterile since large quantities were given. It seemed important nevertheless to determine whether serious blood stream infection occurred.

Blood cultures were obtained on 14 of the dogs. No growth was obtained in three dogs, one of which died. In the other 11, *Streptococcus viridans*, *Bacillus pyocyaneus*, *B. coli*, and *Staphylococcus albus* were found singly or in combination. Usually the growth was not great, being less than one colony per cc. of blood. Nine of the 11 dogs from which positive cultures were obtained survived indefinitely; two died. Those showing the most severe contamination were among the survivors. It would seem that the bacteriaemia present played little or no part in the outcome of the experiments.

Infection of the traumatized muscle probably occurred in some cases, and possibly in many. That this did occur occasionally was shown by the fact that the damaged tissue broke down and discharged in some of the survivors. This evidence of infection was unusual: although swelling of the legs was maximal the day after trauma was applied, it rapidly subsided without apparent complication.

Discussion

The suddenness of the deterioration in the condition of many of our animals following trauma was remarkable. In such cases the blood pressure was well maintained—usually above 100 mm. Hg—for several hours, with a heart rate about 200. Consciousness was usually present. Suddenly the pressure fell, often without a warning increase in pulse rate, and if transfusion was not instituted quickly death occurred within an hour. This sudden failure of cardiovascular compensatory mechanisms was reminiscent of the "break" described by Anderson, Cleghorn, Macleod, and Peterson (1) in the eviscerate, decerebrate cat. In their animals the decline in blood pressure was correlated with a sharp increase in the lactic acid concentration of the blood and a concurrent fall in alkali reserve. While no estimations of these constituents were obtained in the present experiments it is known that such changes do occur in both humans and animals in 'shock' (3, 9, 11), probably as a consequence of the reduced blood volume and cardiac output, and splanchnic vasoconstriction curtailing the blood flow to the abdominal organs. The net result is a functional evisceration. Degenerative hepatic changes varying from mild to severe were found in some of our dogs (5). These changes were attributed

to reduction in blood flow, chiefly from the portal system whence the liver derives 80% of its oxygen (12, 13, 14).

Hypoglycaemia (8) may have been the chief cause of death in some cases. The fact that glucose administration did not prolong life and that some dogs died despite high blood sugar levels indicate that the hypoglycaemia probably reflected disturbed metabolic conditions that were more vitally altered in other respects.

Traumatized dogs differ considerably from those that have endured comparable periods of hypotension as a result of bleeding. Clinically, the traumatized animals appear to be sicker than bled dogs. Unconsciousness, lethargy, and weakness persist far longer after trauma than after bleeding even though the blood pressure may be considerably higher in the former. The blood pressure level has not the same prognostic significance in the two groups of animals. Our experiments on bleeding (6) showed that half the animals with a blood pressure at the end of the 90 min. bleeding period of little more than 56% of the initial pressure survived indefinitely without treatment. Traumatized dogs with hypotension of this degree died (8). In the present series of experiments it was also found that, with one exception, transfusion failed to resuscitate dogs when the pressure was less than 70% of the initial pressure; many with higher pressures also died. These observations are taken as indicating that there are factors, probably of a toxic nature, that are present in dogs sustaining extensive muscle trauma that are not present, to the same extent at least, in bled dogs.

The amount of blood substitute given in the present experiments generally exceeded the average local fluid loss found in similar experiments of Solandt and Best (18). In a few dogs, given still larger transfusions, death was not deferred.

The reason for a fall in blood pressure after restoration by transfusion is not clear. There was little or no loss of plasma as judged by the haematocrit. Functions concerned in the maintenance of blood pressure, other than blood volume, must have been failing, for example: cardiac function. Several animals were observed with clinical signs of acute cardiac dilatation. At autopsy it was noted that, not only in these animals but in some others also, the heart was stopped in diastole. Peripheral vascular failure is the other probable cause for circulatory failure in these animals. As suggested above, this may be due to toxins from traumatized muscle. This topic has been ably summarized by Shorr *et al.* (17). A disturbance in the renal humoral pressor mechanism may have contributed to the vascular failure. Dexter and his colleagues (10) have shown that this mechanism is defective in dogs following severe bleeding. Such animals seemed unable to synthesize hypertensinogin rapidly enough, owing to its conversion to hypertensin by the greatly increased amount of renin produced. Another possible cause for impaired hypertensinogin production in our animals lies in the adrenal damage found, for Dexter and others have shown a diminution in hypertensinogin in the blood of adrenalectomized dogs. The peripheral part of the vascular

failure depends in all likelihood then on a combination of factors: direct effect of toxins and indirect effects of renal and adrenal defects.

The value of adrenal cortical steroids in the treatment of shocked dogs with adrenals intact has not been established. Swingle *et al.* (19) believe they are not beneficial. It was not stated whether adrenal damage was observed in their dogs. The fact that adrenal damage did occur in many of our dogs may account for the successful outcome attending the administration of cortical extract in some of our experiments. The amount of hormone employed was in excess of that required to restore adrenalectomized dogs from adrenal insufficiency but it still may have been insufficient to produce the most convincing demonstration of its effectiveness. The evidence referred to is perhaps sufficient explanation for the results obtained. Deficiency of adrenal secretion can be only one of several factors contributing to the circulatory failure in animals with extensive tissue trauma.

The degenerative changes observed in the kidneys (5) were seldom of sufficient extent to signify gross impairment of renal excretory function according to Bywaters (2) who reviewed the sections. This opinion is supported by our observations. Though the urine passed was abnormal it did not differ significantly in the dogs that died and those that survived.

The beneficial effect of administration of very large quantities of water remains unexplained. Transfusions approximated or exceeded the local fluid loss and dogs were well hydrated before the experiments began.

Acknowledgments

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THE R.C.A.M.C. ELECTROMYOGRAPH MARK III[1]

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Abstract

The R.C.A.M.C. Electromyograph Mark III is an apparatus developed under the auspices of the National Research Council of Canada during the war for the study of casualties with peripheral nerve injuries. It was used principally to study the electrical activity of muscles as a sensitive test of their nerve supply and general condition with regards to atrophy, etc. It is now being used not only in the diagnosis and to follow the recovery of nerve injuries, but for the study of muscle activity in various neuromuscular diseases, including poliomyelitis.

The electromyograph consists of (*a*) a high gain, low noise level, wide range calibrated, balanced, push–pull pre-amplifier, with built-in calibrator, (*b*) a cathode ray oscilloscope unit with photographic attachment, and incorporating a nerve and muscle stimulator of variable intensity and duration, and (*c*) a mobile loud speaker cabinet including the speaker power amplifier, battery, and battery charger.

Action potentials from single muscle fibres, or groups of fibres known as the motor unit, are picked up by means of a small finely pointed needle electrode, insulated except at the very tip, thrust through the skin into the muscle. A reference electrode is placed on the skin next to the point of insertion of the needle and a distant grounded electrode is placed on the subject to aid in the elimination of stray electrical interference. Action potentials are then amplified through four stages of condenser coupled amplification. They are then of sufficient magnitude to be clearly observed or photographed on the calibrated screen of the cathode ray oscilloscope, which makes possible accurate measurement of each potential wave, both in voltage and duration. The sound of the muscle action potentials may be simultaneously heard in the loud speaker. With training, diagnosis of muscle conditions may be greatly aided by certain characteristic sounds produced by different kinds of muscle activity.

For example, a denervated muscle gives rise, from single muscle fibres, to continuous low voltage random 'spikes' that produce in the loud speaker a 'crackling' sound recognized as fibrillation. At rest the normal muscle is electrically silent. It gives rise during contraction to action potentials that are much higher and of longer duration. They produce in the loud speaker a knocking sound recognized as a motor unit discharge. During recovery from a nerve injury, and in certain degenerative conditions, the motor unit becomes poorly synchronized or disintegrated producing very complex wave forms that produce a distinctive 'chugging' sound.

The electrical stimulator, which is synchronized with the trace of the oscilloscope, makes it possible to test the responsiveness of single muscles to different forms of electrical current as well as to record the electrical activity of a given muscle in response to stimulation of its motor nerve at a distance. By the use of the same equipment, the nerve impulse can also be followed in its course down the nerve fibre.

Introduction

During the recent war the Royal Canadian Army Medical Corps under the auspices of the National Research Council of Canada, and with the aid of the Royal Canadian Electrical and Mechanical Engineers, developed special apparatus for the study of casualties with peripheral nerve injuries. The

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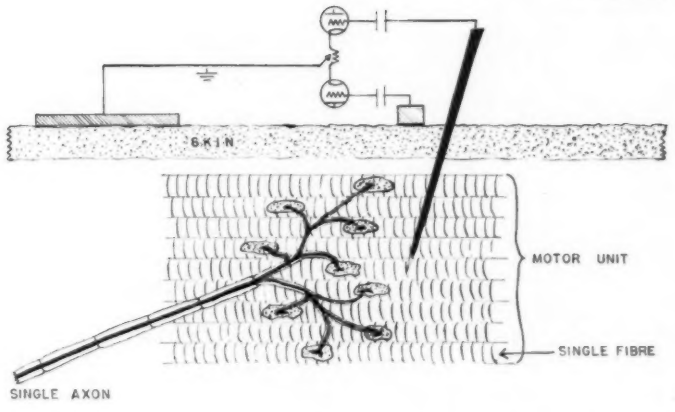
PLATE I



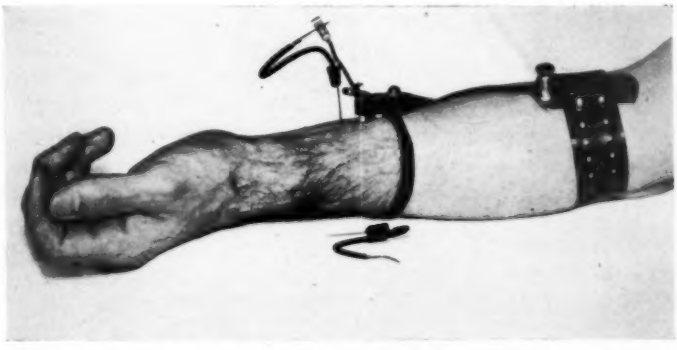


FIG. 1. *Schematic diagram of innervation of muscle by a single motor nerve fibre or axone, with illustration of method of recording muscle action potentials by the use of a single small sharply pointed needle electrode insulated except at the tip. The electrodes attached to the arm are shown in the photograph below.*

most important and generally useful piece of equipment produced was the electromyograph, an apparatus that makes it possible to hear and to see, to photograph and to analyse, the electrical activity of muscle and nerve. This apparatus is similar in principle to that developed by Weddell, Feinstein, and Pattle (9, 10, 11) who first established its clinical usefulness in an extensive series of experimental and clinical studies at the Nerve Injury Centre in Oxford, England.

After confirmation and extension of the experimental and clinical observations made by the Oxford investigators, the electromyograph has been provided to Special Centres for the Treatment of Nerve Injuries in Canada. Owing to increasing interest in the use of electromyography for the study of civilian neuromuscular diseases (most recently poliomyelitis), we wish to present a description of this apparatus. Experimental and clinical results of its use are in preparation for separate publication.

General Description

The action potential from a single muscle fibre or group of fibres (known as the *motor unit*) is picked up by means of a small insulated steel needle electrode thrust through the skin into the muscle. A very sharp pointed needle, such as an embroidery or entomological needle is used. It is insulated, by dipping, with two to three coats of a plastic baking enamel (Tygon), the point remaining uncoated. A reference electrode is placed on the skin as close as possible to the point of insertion of the needle. A third, larger electrode of the type used in electrocardiography, is placed at a distance on the same limb as a ground electrode to eliminate extraneous electrical interference. The needle electrode and its reference on the skin are connected to the grids of a push–pull preamplifier as shown in the schematic diagram of Fig. 1. The photograph below shows the electrodes in place (Fig. 1).

The action potentials from single muscle fibres consist of small monophasic and diphasic transient pulses of 1 to 1.5 millisecond duration and of 0.01 to 0.300 mv. amplitude (Fig. 2). They occur as a spontaneous discharge, called *fibrillation*, only when the nerve supply to a muscle has been completely interrupted and the nerve degenerated. They produce a sound something like the crackling of paper when they are amplified and connected to a loud speaker.

Action potentials from a normal muscle consist only of the synchronized potentials from 100 (more or less) fibres that are fired by a single nerve impulse from a single nerve fibre (shown schematically in Fig. 1).

These *motor unit potentials* are normally diphasic or triphasic transients of about 5 to 7 milliseconds' duration and of 1.0 to 10.0 mv. amplitude (Fig. 2). When many such units are caused to fire together by electrical stimulation of the nerve the potential recorded from the muscle may reach 30 to 40 mv. The normal relaxed muscle is completely 'silent' electrically so that motor unit discharges appear only with voluntary contraction or following electrical stimulation of the nerve, except in certain 'postural' muscles in which complete

relaxation is most difficult. The sound of the motor units is like a sharp knock, or, as many of the soldiers remarked, "like machine-gun fire".

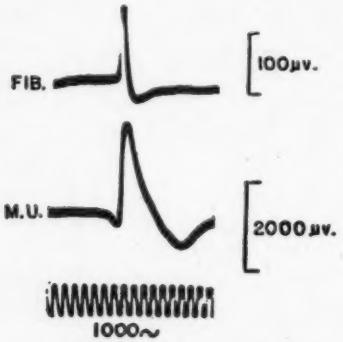


FIG. 2. *Photographs of action potentials from a single muscle fibre (FIB) and from a single motor unit (M.U.) as recorded by the monopolar needle method described in text. Calibrations in milliseconds below, and in microvolts at the right of each tracing.*

After many experimental trials of different types of equipment and the production of two earlier models (2, 3, 4, 5, 6), the final model Mark III Electromyograph comprises the following:

(*a*). A high gain, low noise level, wide range calibrated, balanced, push–pull pre-amplifier, with built-in calibrator.

(*b*). A cathode ray oscilloscope unit with photographic attachment, and incorporating a nerve and muscle stimulator of variable duration and intensity.

(*c*). A mobile loud speaker cabinet and table including the speaker power amplifier, battery and battery charger, and drawers for accessories (Fig. 3).

Pre-amplifier

The pre-amplifier is a balanced push–pull, high gain, calibrated amplifier, comprising three stages of resistance–capacitance coupled amplification (Fig. 4). It may be described as a stable, calibrated, differential, vacuum tube voltmeter. Special attention was paid to the following factors in design and construction:

1. To provide calibrated undistorted control over a wide range of input voltages with linear amplification within the range of the instrument.
2. To eliminate extraneous electrical interference, so that the apparatus might be operated without need for a specially constructed shielded room.
3. To avoid changes in gain due to voltage changes as well as other extraneous influences, and to minimize the possibility of modulation of the signal component by 'hum' voltages.

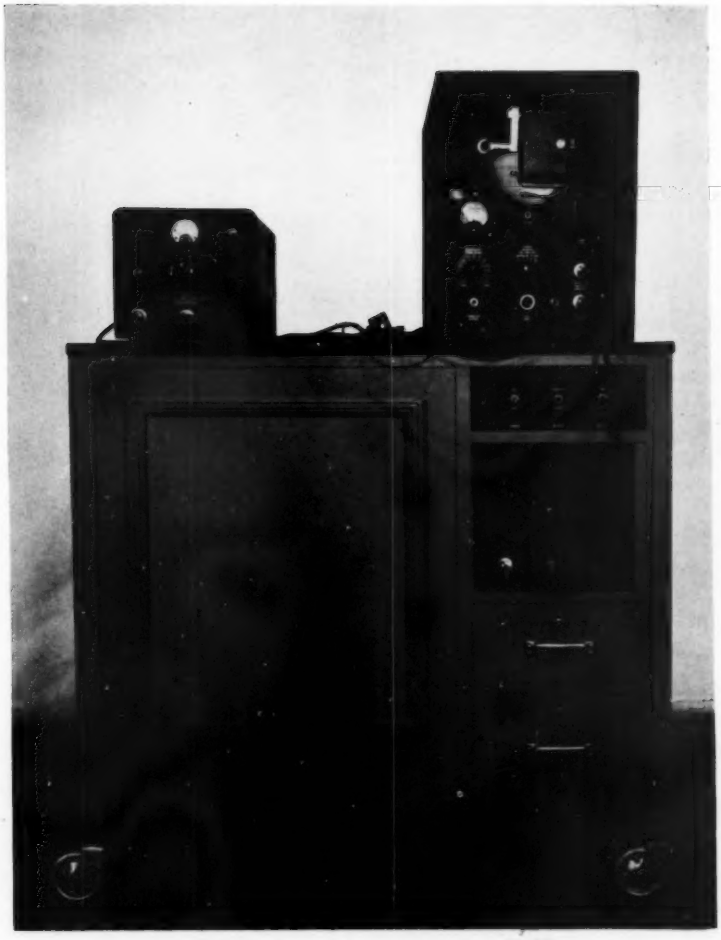


FIG. 3. *Complete assembly of the Electromyograph Mark III with cabinets open ready for use with camera pulled out in place for photography.*

4. To minimize the tube noise component in the signal voltage envelope.
5. To provide adequate frequency response commensurate with stable, high gain amplification of the frequencies encountered.
6. To provide an accurate, stable, calibrating signal voltage source, so that the over-all amplification of the vertical deflection amplification system might be adjusted to fulfil the calibration requirements of the equipment.

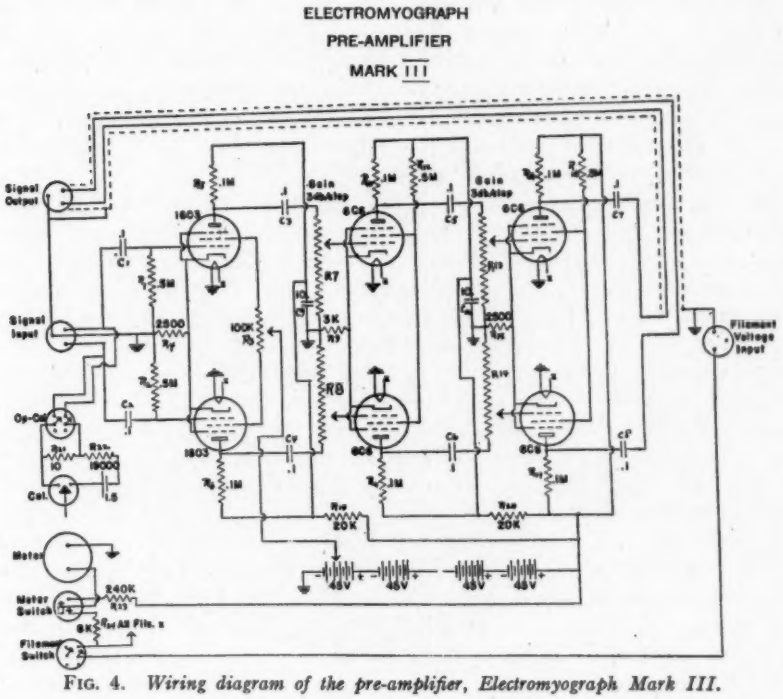


FIG. 4. *Wiring diagram of the pre-amplifier, Electromyograph Mark III.*

With this pre-amplifier, there is possible *linear amplification* of all input voltages between 10 μv. and 100 mv. (a factor of 10,000), a range well above that likely to be encountered in nerve or muscle action potential recording. This was accomplished by a tandem, two section, balanced, 10 step attenuator with a total of 6 db. attenuation per step. With over-all calibration properly standardized (see following), 10 sensitivities were provided as indicated on the master pre-amplifier gain control in millivolts per inch vertical deflection of the cathode ray oscilloscope; 0.1, 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, 12.8, 25.6, and 51.2. Linearity over this wide range was maintained by placing the first pair of balanced sections in the grid circuits of the second stage (Fig. 4, *R*7, *R*8) and the second pair of sections in the grid circuits of the third stage (Fig. 4, *R*13, *R*14). Attenuation is by 3-db. steps in each section.

The calibrator, to provide an accurate and stable signal for standardization of the sensitivity of the entire equipment, was built in to the pre-amplifier input. Placing a toggle switch from the "Op" to the "Cal" position introduces a 10 ohm resistor across the input in place of the subject. (This is also very useful as a convenient method of 'shorting' the input of the pre-amplifier when changing electrodes from one muscle to another.) A push-button switch in the upper right hand corner of the panel is then used to introduce a square wave pulse of 0.8 mv. as a calibrating signal. When the sweep of the cathode ray tube is arrested the vertical deflection of the 'spot' may be adjusted (by the gain set control on the front panel of the P.A. Oscilloscope) to one inch deflection with the pre-amplifier gain control set at 0.8 mv. per inch. Action potentials may then be measured accurately on the grid of the cathode ray tube and translated into millivolts according to the gain setting of the master gain control of the pre-amplifier.

Electrical interference was effectively eliminated, without electrical shielding of the subject, by a screen grid balancing potentiometer in the first stage (Fig. 4, *R*3). Since such interference appears principally as a grid-to-ground signal, careful balancing of the gains of the two input tubes will prevent interference from appearing as a differential signal on the grids of the second stage, since the interference appearing at the output of each tube in the first push–pull stage will be equal in amplitude and 180° out of phase. With a separate low resistance ground connection to the patient most sources of electrical interference encountered may thus be effectively eliminated. The same method is used as an additional method of eliminating the shock artifact when using the stimulator in conjunction with the amplifier–oscillograph system to record nerve or muscle response to electrical stimulation.

Inherent noise and microphonic disturbances have been minimized by careful selection of 'quiet' input tubes that are relatively free from microphonic disturbances (Type 1603) and mounting them on special rubber cushioned ceramic tube sockets. The use of precision wire wound resistors in the first stage and careful shielding of all leads and batteries has helped to reduce inherent noise level to about 2 to 3 μv. peak. This is important since minute voltages of the order of 10 to 20 μv. must occasionally be accurately measured in this work.

The frequency response of the pre-amplifier is flat from 10 to 4000 cycles per second, + or − 1.5 db. The RC time constant is 0.1 sec. This range is adequate for most nerve and muscle action potential work (except when one is interested in the very slow 'after-potential' voltage changes that require a direct coupled amplifier).

Batteries for the pre-amplifier consist of four 45 v. "B" batteries mounted on the chassis, enclosed, and electrically shielded. Filament current is supplied by a 6 v. storage battery located with a trickle charger, in a compartment at the rear of the speaker cabinet. Voltage readings for both "A" and "B" batteries may be obtained from the meter on the front panel, the "B" voltage measured by pressing a push-button switch in the upper left hand corner of

PLATE III

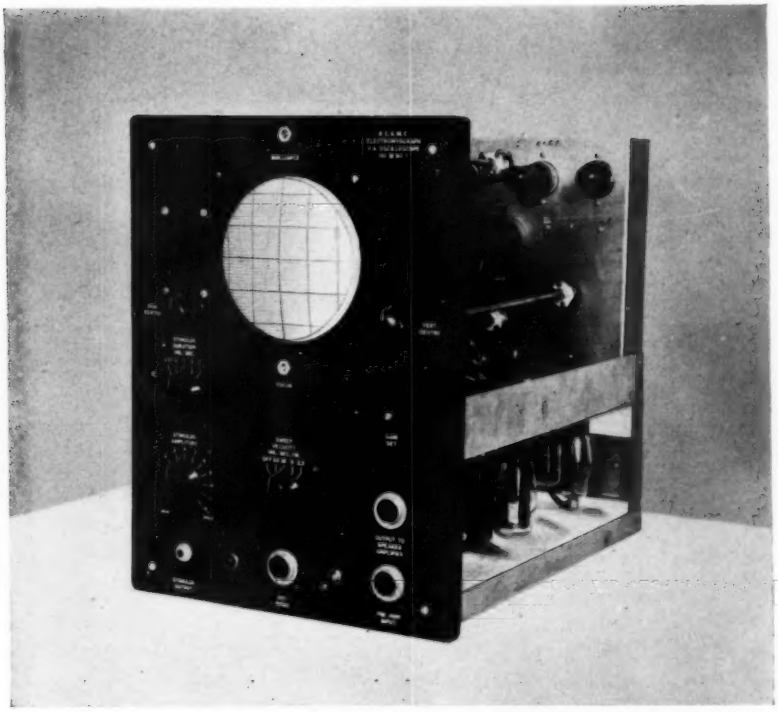


FIG. 5. *The P.A. Oscilloscope, front panel and chassis out of case with camera mount removed.*

the panel. It was found impractical to use an a-c. source for the pre-amplifier, owing to the extensive filtering necessary to reduce the 60 cycle hum modulation to a sufficiently low level when the amplifier was operating at high gain.

P.A. Oscilloscope and Stimulator

In this unit (Fig. 5) the nerve or muscle action potentials receive one more stage of undistorted amplification before reaching the vertical deflection plates of the cathode ray tube, making a total amplification of about one million, with the pre-amplifier. Accurate calibration of vertical deflection in millivolts per inch, by the standardizing control at the input of this unit, and with horizontal deflection velocity or 'sweep' calibrated accurately in milliseconds per inch, voltage and duration of action currents may be measured directly as they appear on the face of the cathode ray tube, which is covered by a transparent 'grid' in tenths of an inch. There is also a square wave stimulator to provide stimuli of different durations and intensities for nerve or muscle stimulation, and a camera for taking records of single sweeps of the cathode ray trace. The various electrically interconnected circuits involved are shown in the wiring diagram (Fig. 6). A brief description of the functional principles of these circuits may be presented under the following headings:

(*a*). Vertical deflection amplifier.

(*b*). Gain set input attenuator.

(*c*). Single sweep time base generator.

(*d*). Multivibrator recurrence frequency generator.

(*e*). Stimulator.

(*f*). Vertical and horizontal positioning circuits.

(*g*). Sweep generator power supply.

(*h*). Power supply for vertical amplifier, stimulator, and multivibrator.

(*a*). *The vertical deflection* amplifier is a single stage push–pull cathode ray tube deflection amplifier employing two type 6AG7 beam power amplifier tubes. These tubes combine high transconductance, with a high plate current that makes it possible to build up a high signal voltage across a low plate load impedance. Linear deflection of the electron beam results, since the spot is deflected off the face of the cathode ray tube before the tubes are driven into the non-linear portion of their characteristic curve. Plate circuit low frequency compensation has been incorporated in the vertical amplifier circuit to provide low frequency response to 10 cycles per second. Precautions have been taken to reduce distributed capacity to a minimum and thus provide a flat frequency response to approximately 10,000 cycles per second.

(*b*). *The gain set input attenuator* provides a fine adjustment of the signal voltage fed to the grids of the push–pull vertical deflection amplifiers. This control permits adjustment of the over-all gain or sensitivity of the vertical deflection amplifier system, which includes the pre-amplifier. Standardized gain settings with respect to the 0.8 mv. peak volts square wave calibrating

signal from the pre-amplifier can be quickly and accurately established by making the 'spot' stationary, setting the pre-amplifier gain control to 0.8 mv. per inch, and adjusting the gain set attenuator for one inch deflection.

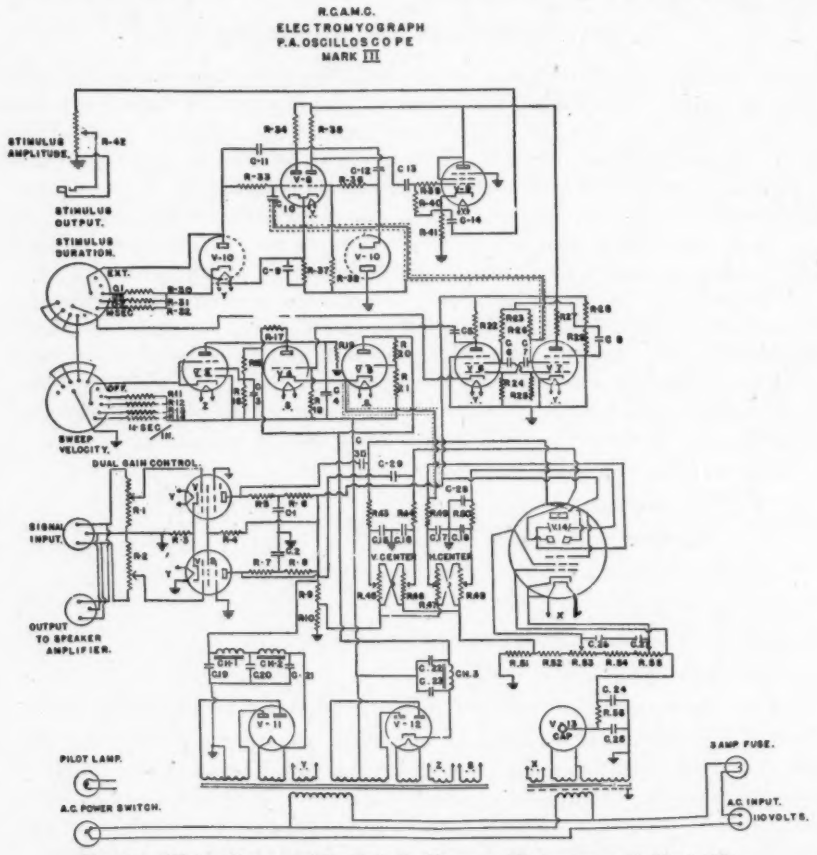


FIG. 6. *Wiring diagram of the P.A. Oscilloscope, Electromyograph Mark III.*

(*c*). *The single sweep time base generator* provides a linear velocity horizontal deflection of the electron beam, at velocities determined by the sweep velocity control. The electron beam is normally deflected to the right side of the cathode ray tube and remains there until caused to make a single excursion across the face of the cathode ray tube by a positive triggering impulse from the multivibrator recurrent frequency generator.

The time base generator employs three tubes:

(1). 6K7—constant current pentode.
(2). 884 —thyratron switch.
(3). 6C5—limiter.

The action of the single sweep time base generator is as follows. The 884 thyratron is normally biased to cut off and is prevented from automatically flashing or conducting by the 6C5 limiter tube, which is connected in parallel with it. A single positive triggering impulse from the recurrence frequency generator raises the grid of the thyratron above the critical grid bias value and the tube conducts heavily, acting as an electronic switch that impresses the output of the sweep power supply across C4, the time base condenser, which very quickly charges to the supply potential.

The 6K7 constant current pentode now comes into action, acting as a resistance that discharges the time base condenser at a linear rate. When the potential difference across the condenser has reached a low value, the cathode of the 6C5 limiter tube assumes a bias that is more negative than that supplied to the grid by the voltage divider R20 and R21. Since the grid of the 6C5 is now positive with respect to the cathode, the tube conducts heavily, effectively by-passing any attempt on the part of the thyratron to develop a potential difference between its plate and cathode that would cause ionization or automatic flashing. The thyratron is now effectively limited to single sweep operation since the 6C5 does not allow it to fire except by a positive change in grid bias, which in this case can only come from the recurrence frequency generator.

Since the recurrence frequency has been established at 7.5 cycles per second we have the single sweep generator operating at a recurrence rate of 7.5 cycles per second, with a pause between sweeps, the pause depending on the sweep velocity.

The control on the front panel provides sweep velocities of 20, 10, 5, and 2.5 milliseconds per inch.

(*d*). *The multivibrator recurrence frequency generator* provides positive triggering pulse to fire the single sweep time base generator, and a negative triggering pulse to initiate the stimulator. The multivibrator establishes the recurrence frequency for the sweep and the stimulator. The multivibrator recurrence frequency has been established at 7.5 cycles per second. This rate was found about optimum to prevent visual superimposition of successive traces on the cathode ray tube.

The multivibrator employs two 6AC7 pentode type tubes, in what is commonly described as an electron coupled multivibrator. The circuit is conventional, but the screen grids of the tubes are used as plates for the performance of the switching function.

A portion of the electron stream in the conducting tube reaches the plate proper because it is made positive by its connection to the power supply. This portion furnishes the output of the multivibrator. The suppressor grids shield the screen and control grids from the plates and prevent changes in the load from affecting the oscillatory circuit. The frequency of oscillation is thus reasonably independent of the output. Since the plate load resistors are of a high value (250 K) and since the 6AC7 is a high transconductance

tube, a square wave, with sharp leading edges, appears at the plate of each tube as it conducts heavily or is driven to cut off.

The output from the appropriate plate of the multivibrator is fed into a differentiator distortion network that produces a very sharp positive triggering pulse of short duration and of sufficient amplitude to trigger the single sweep time base generator.

The stimulator is triggered by the sudden negative swing of voltage appearing at the grid of the other tube in the multivibrator circuit. A slight delay appears between the time the sweep is initiated and the time the onset of the square wave from the stimulator appears on the cathode ray trace, as can be shown by connecting the output of the stimulator to the vertical deflection amplifier.

(*e*). *The stimulator* provides a negative going square wave voltage of controlled duration and amplitude with a recurrence frequency of 7.5 cycles per second. It is used for nerve or muscle stimulation external to, or in conjunction with, the electromyograph MK III. The stimulus duration can be controlled by the front panel control with durations of 1.0, 0.5, and 0.2 milliseconds. An additional stimulus, 'galvanic' in nature, with a duration of 0.1 sec. and a recurrence frequency of two cycles per second can be obtained by turning the stimulus duration control to the "O" position. The stimulus amplitude control on the front panel controls the amplitude of stimulus and provides a negative going square wave with amplitudes of 0 to −90 v. A separate Wagner earth balancing circuit and a vernier intensity control are provided in a separate shielded box for use with direct nerve stimulation and recording of nerve or muscle action potentials.

The stimulator employs three tubes:

(1). 6N7 —one-shot multivibrator.
(2). 6H6 —duration limiter.
(3). 6AG7—cathode follower.

The 6N7 one-shot multivibrator is a modification of the Eccles Jordan circuit that accomplishes a complete cycle when triggered with a negative pulse. It is essentially a two stage resistance–capacitance coupled amplifier with one tube normally conducting and the other tube cut off. The balanced condition of the circuit is established by the arrangement for biasing the tubes.

The grid of the left hand triode is connected to its cathode and since it has zero bias the tube is normally conducting heavily. The grid of the right hand triode is tied to ground. The current flowing through the left hand triode develops a high bias voltage across *R*37 that causes the right hand triode to be cut off. A negative triggering pulse from the multivibrator will cause the left hand triode to be cut off. Since the right hand triode now has no bias voltage developed across *R*37 it will conduct heavily, causing a large voltage drop to appear at the plate of the right hand triode. A short time interval, later, depending on the value of *R* 30, 31, 32, equilibrium condition will be re-established in which the left hand triode is conducting heavily and

right hand triode is suddenly cut off, resulting in a sudden rise in voltage at the plate of this tube. A complete cycle has now been made in which a negative square wave of voltage has been produced at the plate of the right hand triode.

The function of the 6H6 duration limiter is to stabilize the grid voltage excursion of both triodes so that the stimulus length will remain constant.

The output from the one-shot multivibrator is fed to the grid of the 6AG7 cathode follower. This circuit has been employed since the output of such a device has a very low impedance, and consequently is not materially affected by changes in load placed across its output. Distortion of wave form due to reactive load placed upon the output of the stimulator is thus minimized. The 6AG7 is normally conducting heavily and the negative square wave from the one-shot multivibrator applied to its grid causes it to conduct less heavily for a period determined by the square wave stimulus duration. The decrease in current through *R*41 produces a negative square wave voltage drop that is fed to *R*42, the stimulus amplitude control on the front panel through condenser C-14.

External control of the sweep is provided by an additional position on the stimulus duration control. In this position the recurrence frequency generator is cut off, resulting in cessation of operation of both the single sweep time base generator and the stimulator. By providing an external position triggering pulse to the grid of the thyratron in the time base generator, the sweep will function normally, with velocity determined by the sweep velocity control settings, and recurrence frequency determined by the recurrence frequency of the external apparatus.

This provision is made in case one wishes to synchronize the shutter of a camera with single sweeps or in case a different type of nerve or muscle stimulator is to be used in conjunction with the recording of nerve or muscle action potentials.

Photographic Recording

Photographic records of single sweeps of the electron beam on the face of the cathode ray tube are obtained by the use of a standard roll film camera, preferably of small size. Vest pocket or 35 mm. size is most convenient but larger size cameras may be employed. It is necessary that the camera have a good shutter with accurate exposure times down to as low as 1/5 sec. The lens must be of good quality with aperture of f. 3.5 or better. A 'portrait' lens attachment is used with the standard lens, so that the image of the tube face may be made to occupy the entire film. With the camera on a telescopic mount, it can be quickly placed at the proper distance from the tube face (5 to 7 in.) whenever photographic records are desired, and swung out of the way to provide better visibility when not in use.

To obtain records of single sweeps one has only to set the exposure time according to the recurrence rate of the sweep, e.g., with the recurrence rate at 7 per sec. the exposure time is set at 1/7 sec. and one sweep will be recorded for each exposure.

Speaker Power Amplifier

This unit comprises a two stage push–pull resistance–capacitance coupled power amplifier, and power supply. The circuit is conventional with the possible exception of the plate circuit compensation in the first stage. The operation is Class A. Low hum level in the output is the result of very good filtering in the power supply.

The frequency response is normally flat from approximately 10 cycles per second to 10,000 cycles per second, however by switching in the low frequency booster, the lows may be accentuated and the high frequencies slightly attenuated.

The power output is 6 w. undistorted.

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